BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/2015**
SECTION: DRUGS	**LAST REVIEW DATE: 5/19/2022**
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FARYDAK® (panobinostat)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

FARYDAK® (panobinostat)

Criteria:

- **Criteria for initial therapy:** Farydak (panobinostat) is considered ***medically necessary*** when of **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
    a. Multiple myeloma (MM) for relapse or progressive disease in an individual who has received at least 2 prior regimens, including Velcade (bortezomib) and an immunomodulatory agent (Revlimid (lenalidomide), Pomylast (pomalidomide), or Thalomid (thalidomide))

    b. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. When approved for MM, Farydak (panobinostat) will be used in combination with **ANY** of the following:
    a. Velcade (bortezomib) and dexamethasone
    b. Kyprolis (carfilzomib)
    c. Revlimid (lenalidomide) and dexamethasone

5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Negative pregnancy test in a woman of childbearing potential
    b. Electrocardiogram to verify QT_cF is < 450 msec
    c. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1

6. Individual does not have an active infection

7. Will not be used in an individual with severe hepatic impairment

8. Will not be used in an individual with end stage renal disease or individual on dialysis

9. There are no significant interacting drugs
    a. Will not be used with strong 3A4 inhibitors (See Definitions section)
    b. Will not be used with strong 3A4 inducers (See Definitions section)
    c. Sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index (See Definitions section)
    d. QT prolonging drugs (See Definitions section)

10. Individual does not have any of the following:
    a. Recent myocardial infarction
    b. Unstable angina
    c. Corrected QT interval greater than 450 msec

FARYDAK® (panobinostat)

d. Clinically significant ST-segment or T-wave abnormalities

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Farydak (panobinostat) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

3. Dose is at least 10 mg 3 times per week

4. Individual has been adherent with the medication

5. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Severe or life-threatening diarrhea despite use of anti-diarrheal treatment
        ii. Gastrointestinal hemorrhage
        iii. Pulmonary hemorrhage
        iv. Liver toxicity
        v. Thrombocytopenia that does not improve despite the recommended treatment modifications
        vi. Requires repeated platelet transfusions
        vii. Neutropenia that does not improve despite dose modifications and use of colony-stimulating factors
        viii. QTcF greater than 480 msec or has clinically significant baseline ST-segment or T-wave abnormalities that do not resolve

6. Individual does not have an active infection

7. Will not be used in an individual with severe hepatic impairment

8. Will not be used in an individual with end stage renal disease or individual on dialysis

9. There are no significant interacting drugs
    a. Will not be used with strong 3A4 inhibitors (See Definitions section)
    b. Will not be used with strong 3A4 inducers (See Definitions section)
    c. Sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index (See Definitions section)

FARYDAK® (panobinostat)

d. QT prolonging drugs (See Definitions section)

10. Individual does not have any of the following:
    a. Recent myocardial infarction
    b. Unstable angina
    c. Corrected QT interval greater than 450 msec
    d. Clinically significant ST-segment or T-wave abnormalities

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Farydak (panobinostat), a histone deacetylase inhibitor, used in combination with Velcade (bortezomib) and Dexamethasone, is indicated for the treatment of patients with multiple myeloma (MM) who have received at least 2 prior regimens, including Velcade (bortezomib) and an immunomodulatory agent [such as Thalomid (thalidomide), Revlimid (lenalidomide), Pomalyst (pomalidomide)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

MM is a malignancy of plasma cells in the bone marrow. Malignant monoclonal plasma cells accumulate in the bone marrow and produce a monoclonal protein (usually IgG or IgA which are often referred to as M or myeloma proteins) that causes disruption of normal bone marrow function, destruction and invasion of bone surrounding the bone marrow cavity, production and release of M-proteins from the myeloma cells into the blood stream and/or into the urine, and a reduction of normal immune function. MM makes up 10-15% of all hematologic malignancies.

MM is a genetically complex disease that develops through several steps over time and as a result has various clinical presentations or phases. The earliest phase is monoclonal gammopathy of undetermined significance (MGUS), is an indolent, asymptomatic premalignant phase with a small clonal population of plasma cells within the bone marrow of <10%. MGUS is considered the initial event in the pathogenesis of MM. Progression to myeloma is approximately 1% per year. The next phase is smoldering multiple myeloma (SMM), another asymptomatic phase distinguished from MGUS by a greater tumor cell content of >10% and an average risk of progression to myeloma of 10% per year for the first five years. The myeloma phase is recognized when malignant clones cause clinically relevant end-organ damage such as the features known as CRAB (hypercalcemia, renal dysfunction, anemia, and bone lesions, including bone pain and fractures). Other manifestations include infection, neurologic symptoms (lethargy, headaches, confusion, depression and other), clotting abnormalities and hyperviscosity. The final phase is plasma cell leukemia (PCL).

FARYDAK® (panobinostat)

MM is characterized by multiple relapses and progressive refractoriness to available therapies. There is no cure. The choice of primary therapy is based on whether a patient is a candidate for a stem cell transplant. Drug therapy is used to bridge eligible patients to an autologous stem cell transplant (ASCT).

Agents from four different classes are combined with one another or with corticosteroids and/or various generic chemotherapy medications to make up a MM drug regimen. Medication drug classes include: *Chemotherapy:* liposomal doxorubicin (Doxil), melphalan, cyclophosphamide, vincristine, etoposide, cisplatin, others; *HDAC inhibitor:* panobinostat (Farydak); *Immunomodulators:* lenalidomide (Revlimid), pomalidomide (Pomalyst), thalidomide (Thalomid); *Proteasome inhibitors:* bortezomib (Velcade) and carfilzomib (Kyprolis).

Farydak (panobinostat) is a histone deacetylase (HDAC) inhibitor that blocks the enzymatic activity of HDAC. HDAC inhibitors act by increasing the productions of proteins that slow cell division and cause cell death. They have shown limited efficacy when used alone. HDAC catalyzes the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. *In vitro*, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Panobinostat shows more cytotoxicity towards tumor cells compared to normal cells.

Definitions:

QT interval correction Fridericia method
QT interval divided by the cube root of the RR interval:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Penta-refractory disease is defined for multiple myeloma as refractory to all of the following:

- An anti-CD38 monoclonal antibody (e.g., Darzalex (daratumumab), Sarclisa (isatuximab))
- Kyprolis (carfilzomib)
- Pomalyst (pomalidomide)
- Revlimid (lenalidomide)
- Velcade (bortezomib)

Strong 3A4 inhibitors:
Atazanavir, boceprevir, clarithromycin, conivaptan, darunavir, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, voriconazole, and others

Strong CYP3A inducers:
Rifampin phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids, and others

FARYDAK® (panobinostat)

Sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index:
Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, and venlafaxine, thioridazine and pimozide

Concomitant use of drugs that are known to prolong the QT interval:
Anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that are known to prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide).

Resources:

Farydak (panobinostat) product information, revised by Secura Bio, Inc. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 11, 2022.

Laubach JP. Multiple myeloma: Treatment of third or later relapse. In: UpToDate, Rajkumar SV, Connor RF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated March 10, 2022. Accessed May 11, 2022.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple myeloma Version 5.2022 – Updated March 09, 2022. Available at https://www.nccn.org. Accessed May 11, 2022.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.