INDICATION

FARYDAK® (panobinostat) capsules, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 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.

IMPORTANT SAFETY INFORMATION

WARNING: FATAL AND SERIOUS TOXICITIES: SEVERE DIARRHEA AND CARDIAC TOXICITIES

Severe diarrhea occurred in 25% of FARYDAK treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt FARYDAK and then reduce dose or discontinue FARYDAK.

Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving FARYDAK. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.

Diarrhea

- Severe diarrhea occurred in 25% of patients treated with FARYDAK. Diarrhea of any grade occurred in 68% of patients treated with FARYDAK compared with 42% of patients in the control arm. Diarrhea can occur at any time. Ensure patients have antidiarrheal medications on hand, and initiate antidiarrheal medication at the onset of diarrhea
- Monitor hydration status and electrolyte blood levels at baseline, and weekly (or more often as clinically indicated) during therapy, and correct to prevent dehydration and electrolyte disturbances
- Interrupt FARYDAK at the onset of moderate diarrhea (4-6 stools/day)
- For life-threatening diarrhea (grade 4), permanently discontinue FARYDAK and bortezomib
- For severe diarrhea (≥7 stools/day), or IV fluids or hospitalization required (grade 3), interrupt FARYDAK and bortezomib until resolved and restart both at reduced doses
- For moderate diarrhea (4-6 stools/day, grade 2), interrupt FARYDAK until resolved and restart at same dose. Consider interruption of bortezomib until resolved and restart at same dose

Cardiac Toxicities

- Arrhythmias occurred in 12% of patients treated with FARYDAK compared with 5% of patients in the control arm. Cardiac ischemic events occurred in 4% of patients treated with FARYDAK compared with 1% of patients in the control arm

- Do not initiate FARYDAK treatment in patients with history of recent myocardial infarction or unstable angina

- ECG abnormalities such as ST-segment depression and T-wave abnormalities occurred more frequently in patients receiving FARYDAK compared with the control arm: 22% vs 4% and 40% vs 18%, respectively

- FARYDAK may prolong QT interval. Do not initiate treatment with FARYDAK in patients with a QTcF >450 msec or clinically significant baseline ST-segment or T-wave abnormalities

- Arrhythmias may be exacerbated by electrolyte abnormalities. If during treatment with FARYDAK the QTcF increases to ≥480 msec, interrupt treatment. Correct any electrolyte abnormalities. If QT prolongation does not resolve, permanently discontinue treatment. Obtain ECG at baseline and periodically during treatment. Monitor electrolytes during treatment with FARYDAK, and correct abnormalities as clinically indicated

Hemorrhage

- Fatal and serious cases of gastrointestinal and pulmonary hemorrhage occurred
- In the phase 3 registration trial, 5 patients receiving FARYDAK, compared with 1 patient in the control arm, died due to a hemorrhagic event. All 5 patients had grade ≥3 thrombocytopenia at the time of the event
- Grade 3/4 hemorrhage was reported in 4% of patients treated with FARYDAK and 2% of patients in the control arm
- Monitor platelet counts and transfuse as needed

Myelosuppression

- FARYDAK causes myelosuppression, including severe thrombocytopenia, neutropenia, and anemia. Obtain a baseline CBC, and monitor the CBC weekly during treatment (or more often if clinically indicated or in patients >65 years of age)

- Thrombocytopenia

    - In the phase 3 registration trial, 67% of patients treated with FARYDAK developed Grade 3/4 thrombocytopenia compared with 31% in the control arm
    - Thrombocytopenia led to treatment interruption and/or dose modification in 31% of patients receiving FARYDAK
    - For patients receiving FARYDAK, 33% required platelet transfusion
    - For patients with platelet count $<50 \times 10^9$/L with bleeding (grade 3) or $<25 \times 10^9$/L (grade 4)
        - Interrupt FARYDAK therapy and monitor platelets at least weekly until $\geq 50 \times 10^9$/L, and restart at reduced dose
        - Interrupt bortezomib until thrombocytopenia resolves $\geq 50 \times 10^9$/L
            - If only 1 dose of bortezomib was omitted prior to correction to these levels, restart bortezomib at same dose

        - If ≥2 doses were omitted consecutively, or within the same cycle, restart at a reduced dose
    - For patients with platelet count <50 x 10^9/L (grade 3), maintain FARYDAK and bortezomib doses and monitor platelet counts at least weekly
    - For patients with severe thrombocytopenia, consider platelet transfusions
    - Discontinue FARYDAK if thrombocytopenia does not improve despite the recommended treatment modifications or if repeated platelet transfusions are required

- Neutropenia
    - Severe neutropenia occurred in 34% of patients treated with FARYDAK compared with 11% of patients in the control arm
    - Neutropenia led to treatment interruption and/or dose modification in 10% of patients receiving FARYDAK
    - Use of granulocyte-colony stimulating factor (G-CSF) was 13% in patients treated with FARYDAK
    - For patients with ANC <0.5 x 10^9/L (grade 4)
        - Interrupt FARYDAK and bortezomib therapy until ANC is ≥1.0 x 10^9/L. Restart FARYDAK at reduced dose
        - If only 1 dose of bortezomib was omitted prior to correction to these levels, restart at same dose. If ≥2 doses of bortezomib were omitted consecutively, or within the same cycle, restart at reduced dose
    - For patients with ANC <1.0 x 10^9/L (grade 3) and febrile neutropenia (any grade)
        - Interrupt FARYDAK and bortezomib therapy until febrile neutropenia is resolved and ANC >1.0 x 10^9/L
        - Restart FARYDAK at reduced dose
        - If only 1 dose of bortezomib was omitted prior to correction to these levels, restart at same dose. If ≥2 doses of bortezomib were omitted consecutively, or within the same cycle, restart at reduced dose
    - For patients with ≥2 occurrences of ANC between 0.5 – 0.75 x 10^9/L (grade 3)
        - Interrupt FARYDAK therapy until ANC ≥1.0 x 10^9/L, and restart at same dose
        - Maintain bortezomib dose
    - For patients with ANC between 0.75 – 1.0 x 10^9/L (grade 3)
        - Maintain FARYDAK and bortezomib doses
    - For grade 3 or 4 neutropenia, consider dose reduction and/or the use of growth factors
    - Discontinue FARYDAK if neutropenia does not improve despite dose modifications, CSF, or in case of severe infection
- Anemia
    - For patients with hemoglobin <8 g/dL (grade 3), interrupt FARYDAK until hemoglobin ≥10 g/dL. Restart at reduced dose

Infections

- Severe infections occurred in 31% of patients (including 10 deaths) treated with FARYDAK compared with 24% of patients (including 6 deaths) in the control arm

- FARYDAK treatment should not be initiated in patients with active 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 FARYDAK

Hepatotoxicity

- Hepatic dysfunction, primarily elevations in aminotransferases and total bilirubin, occurred in patients treated with FARYDAK
- Monitor liver function prior to and regularly during treatment. If abnormal liver function tests are observed, consider dose adjustments. Follow patient until values return to normal or pretreatment levels
- Avoid use in patients with severe hepatic impairment
- Reduce the starting dose of FARYDAK to 15 mg or 10 mg in patients with mild or moderate hepatic impairment, respectively

Embryo-Fetal Toxicity

- FARYDAK can cause fetal harm when administered to a pregnant woman
- If FARYDAK is used during pregnancy, or if the patient becomes pregnant while taking FARYDAK, the patient should be apprised of the potential hazard to the fetus
- Advise females of reproductive potential to avoid becoming pregnant while taking FARYDAK
- Advise sexually active females of reproductive potential to use effective contraception while taking FARYDAK, and for at least 3 months after the last dose of FARYDAK
- Advise sexually active men to use condoms while on treatment, and for at least 6 months after their last dose of FARYDAK

Drug Interactions

- Reduce dose to 10 mg when coadministered with strong CYP3A inhibitors. Instruct patients to avoid star fruit, pomegranate or pomegranate juice, and grapefruit or grapefruit juice
- Avoid the concomitant use of strong CYP3A inducers
- Avoid coadministration with sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index. If concomitant use of CYP2D6 substrates is unavoidable, monitor patients frequently for adverse reactions
- Concomitant use of antiarrhythmic medicines, and other drugs that are known to prolong the QT interval, is not recommended. Antiemetic drugs with known QT-prolonging risk can be used with frequent ECG monitoring

Adverse Reactions

- The most common adverse reactions (incidence of at least 20%) in clinical studies are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting
- The most common nonhematologic laboratory abnormalities (incidence ≥40%) are hypocalcemia, hypophosphatemia, hypoalbuminemia, hypokalemia, hyponatremia, and increased creatinine. The most common hematologic laboratory abnormalities (incidence ≥60%) are thrombocytopenia, lymphopenia, leukopenia, neutropenia, and anemia
- Serious adverse events (SAEs) occurred in 60% of patients in the FARYDAK arm. The most frequent (≥5%) treatment-emergent SAEs reported for patients treated with FARYDAK were pneumonia, diarrhea, thrombocytopenia, fatigue, and sepsis

Please see full Prescribing Information, including Boxed WARNING, for FARYDAK® (panobinostat) capsules.