RDL DRUG REVIEW

Proprietary Name: Farydak®
Common Name: panobinostat lactate
PDL Category: Antineoplastics

Comparable Products	Recommended Drug List Status
Pomalyst	Non-Recommended
Revlimid	Recommended

Summary

Indications and Usage: In combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma (MM) who have received ≥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.

While a specific pregnancy category has not been assigned, the risk summary indicates that Farydak® can cause fetal harm when given to pregnant women, as it was teratogenic in rats and rabbits. Pregnancy testing in women of childbearing potential should be performed prior to starting treatment and intermittently during treatment. Furthermore, it is recommended that this population use effective contraception during treatment and for ≥1 month after the last dose of Farydak®. The safety and efficacy of use in children have not been established.

Dosage Forms: Capsules: 10mg, 15mg, and 20mg

Recommended Dosage: Prior to starting treatment and during treatment, monitoring should include obtaining a complete blood count (CBC), an ECG (to verify that the QTcF is <450msec prior to starting treatment), and serum electrolytes (any abnormal electrolyte value should be corrected prior to starting treatment). Please refer to the prescribing information for further specific information.

The recommended starting dose is 20mg PO every other day for 3 doses per week in weeks 1 and 2 of each 21 day cycle for up to 8 cycles. Consider continuing treatment for another 8 cycles in those with clinical benefit who do not experience unresolved severe or medically significant toxicity, for a total treatment duration of up to 16 cycles (48 weeks). It should be given in combination with bortezomib and dexamethasone as per the recommended dosing schedule found in the prescribing information.

Management of adverse drug reactions may require treatment interruption and/or dose reductions. Refer to the prescribing information for further specific information.

The safety and efficacy of use in those with hepatic impairment has not been studied; however, a pharmacokinetic study suggested that there were increases in AUC of panobinostat by 43% in those with mild impairment and 105% in those with moderate hepatic impairment. Therefore, it is recommended to reduce the starting dose in

those with mild or moderate and avoid use in severe hepatic impairment. Additionally, it is recommended to monitor this population for adverse events. While dose adjustments are not required in those with mild to severe renal impairment, use has not been studied in those with end stage renal disease (ESRD) or dialysis.

Drug Interactions: Panobinostat is a CYP3A substrate and inhibits CYP2D6. It is also a P-gp transporter system substrate. It is recommended to reduce the starting dose of Farydak® to 10mg if given concomitantly with strong CYP3A inhibitors (e.g. boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole). Grapefruit and grapefruit juice, star fruit, and pomegranate or pomegranate juice should be avoided with Farydak®. The concomitant use of strong CYP3A inducers should be avoided with Farydak®. It is recommended to avoid the concomitant use with sensitive CYP2D6 substrates (i.e. atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, and venlafaxine) or CYP2D6 substrates with a narrow therapeutic index (i.e. thioridazine, pimozide); however, if concomitant use is unavoidable, frequently monitor for adverse events. The concomitant use of anti-arrhythmic medications (including but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other drugs known to prolong the QT interval (including but not limited to chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil, and pimozide) are not recommended. (Nevertheless, anti-emetic drugs with known QT prolongation risk, such as ondansetron and dolasetron, can be used with frequent ECG monitoring).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Farydak® plus bortezomib/dexamethasone) minus reported % incidence for placebo plus bortezomib/dexamethasone. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than its comparators.* The most frequently reported adverse events included arrhythmia (10%), diarrhea (60%), nausea (35%), vomiting (25%), fatigue (48%), peripheral edema (>28%), pyrexia (24%), weight decreased (11%), and decreased appetite (27%). Severe infections (6%) and arrhythmias (7%) were also reported.

Reported lab abnormalities included thrombocytopenia (66%), anemia (43%), neutropenia (64%), leukopenia (73%), lymphopenia (42%), blood creatinine increased (39%), hypokalemia (45%), hypophosphatemia (51%), hyponatremia (42%), hyperbilirubinemia (>20%), hypocalcemia (65%), hypoalbuminemia (61%), hyperphosphatemia (>28%), and hypermagnesemia (26%).

Contraindications: There are none listed.

Manufacturer: Novartis

Analysis: Panobinostat lactate, the active ingredient of Farydak®, is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDAC. This inhibition resulted in the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Farydak® does have a box warning regarding the increased risk of fatal and serious toxicities, including severe diarrhea and cardiac toxicities. Severe diarrhea occurred in 25% of those treated with Farydak® in clinical trials. Thus, it is recommended to monitor for symptoms, use anti-diarrheal treatment, interrupt Farydak® treatment and then reduce the dose or discontinue Farydak®. In addition, severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have been reported with Farydak® use. It is recommended to obtain an ECG and electrolytes at baseline and monitor periodically.

The safety and efficacy of Farydak® were assessed in a randomized, double-blind, placebo-controlled study that included patients (N=768) with relapsed MM who had received 1-3 prior lines of therapy. Farydak® and placebo were given in combination with bortezomib and dexamethasone. The primary endpoint was progression-free survival (PFS). In the overall trial population, the median PFS was 12 months in the Farydak® arm vs 8.1 months in the placebo arm (hazard ratio [HR] 0.63). At the interim analysis, overall survival was not statistically different between treatment groups. Nevertheless, approval of Farydak® was based on the safety and efficacy in a prespecified sub-group analysis of 193 subjects who had received prior treatment with bortezomib and an

immunomodulatory agent and a median of 2 prior therapies. The median PFS in this population was 10.6 months with the Farydak® group vs 5.8 months in the placebo group (HR 0.52). In this sub-group, the overall response rate (ORR) can be seen in the table below (adapted from the prescribing information).

	Farydak® group (N=94)	Placebo group (N=99)
Overall Response Rate (ORR)	58.5%	41.4%
Complete Response Rate	8.5%	2.0%
Near Complete Response Rate	13.8%	7.1%
Partial Response Rate	36.2%	32.3%

Place in Therapy: Farydak® was FDA approved under accelerated approval for multiple myeloma (MM) to be used in combination with bortezomib and dexamethasone in adults who have received ≥2 prior regimens, including bortezomib and an immunomodulatory agent. Major safety issues and concerns are included in its box warning.

It is recommended that Farydak® be added to the Recommended Drug List as a non-recommended drug, as it is not intended as a first-line treatment option.

RDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Farydak [package insert]. East Hanover, NJ: Novartis; 2015.