PDL DRUG REVIEW

Proprietary Name: Ninlaro®
Common Name: ixazomib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Farydak	Non-Recommended
Pomalyst	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Ixazomib citrate, a prodrug, is hydrolyzed under physiological conditions to its biologically active form, ixazomib. Ixazomib, the active ingredient of Ninlaro®, is a reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. In vitro, ixazomib induced apoptosis of multiple myeloma cell lines and showed cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone.

Indication: In combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

While there is no pregnancy category associated with this product, the risk summary indicates that Ninlaro® can cause fetal harm when administered to a pregnant woman. It is recommended that women avoid becoming pregnant while being treated with Ninlaro® and that woman are advised of the potential risk to a fetus. Males and females of childbearing potential must use effective contraceptive measures during treatment and for 90 days following treatment discontinuation. The safety and efficacy of use have not been established in the pediatric population.

Dosage Forms: Capsules: 2.3mg, 3mg, 4mg

Recommended Dosage: The recommended starting dose of Ninlaro® is 4mg PO QW on days 1, 8, and 15 of a 28-day treatment cycle in combination with lenalidomide (25mg QD on days 1-21 of a 28 day cycle) and dexamethasone (40mg on days 1, 8, 15, and 22 of a 28-day cycle). Ninlaro® should be taken at least one hour before or at least 2 hours after food but with water. Treatment should be continued until disease progression or unacceptable toxicity. For addition information regarding lenalidomide and dexamethasone, please refer to their corresponding prescribing information.

Prior to starting a new cycle of therapy, it is recommended that: the absolute neutrophil count be ≥1,000/mm^3, platelet count be ≥75,000/mm^3, and non-hematologic toxicities, at the physician's discretion, be recovered to patient's baseline condition or Grade 1 or lower.

It is recommended to reduce the starting dose of Ninlaro® to 3mg in patients with moderate or severe hepatic impairment, as well as with patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis. Please refer to the prescribing information regarding specific recommendations/actions for Ninlaro® dose modifications due to adverse reactions.

Drug Interactions: It is recommended to avoid concomitant use of Ninlaro® with strong CYP3A inducers, such as rifampin, phenytoin, carbamazepine, and St. John's Wort.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ninlaro® plus lenalidomide/dexamethasone) minus reported % incidence for placebo plus lenalidomide/dexamethasone. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included upper respiratory tract infections (5%), peripheral neuropathies (7%), diarrhea (6%), constipation (9%), nausea (5%), vomiting (11%), rash (8%), back pain (5%), and edema peripheral (7%). Reported lab abnormalities include thrombocytopenia (24%) and neutropenia (1%). Eye disorders (10%) were also reported, with the most common reported being blurred vision (3%), dry eye (4%), and conjunctivitis (5%).

Reported adverse events that may require dose modifications include thrombocytopenia, neutropenia, rash, peripheral neuropathy, or other non-hematological toxicities.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company

Analysis: There was one randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of Ninlaro® that included patients (N=722) with relapsed and/or refractory multiple myeloma who had received at least one prior treatment. Patients who were refractory to lenalidomide or proteasome inhibitors were excluded from the study. Patients were randomized to Ninlaro®, lenalidomide, and dexamethasone or to placebo, lenalidomide, and dexamethasone, and they continued treatment until disease progression or unacceptable toxicity.

The efficacy of Ninlaro® was assessed by progression-free survival (PFS) per the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria per a blinded independent review committee. Results suggested that there was a statistically significant improvement in PFS of the Ninlaro® regimen as compared to the placebo regimen. Results are illustrated in the table below.

	Ninlaro® regimen	Placebo regimen
Progression-Free Survival (PFS)		
PFS Events, N (%)	129 (36%)	157 (43%)
Median, months	20.6	14.7
Hazard Ratio, P-value	0.74; p=0.012	
Response Rate		
Overall Response Rate, N (%)	282 (78%)	259 (72%)
Complete Response	42 (12%)	24 (7%)
Very Good Partial Response	131 (36%)	117 (32%)
Partial Response	109 (30%)	118 (33%)

The median time to response was 1.1 months with the Ninlaro® regimen as compared to 1.9 months with the placebo regimen. In addition, the median duration was response was 20.5 months as compared to 15 months, respectively.

A planned interim overall survival (OS) analysis was performed, with 35% of the required number of deaths for final OS analysis. An overall survival benefit was not demonstrated, as there were 81 deaths in the Ninlaro® regimen as compared with 90 deaths in the placebo regimen.

Place in Therapy: Ninlaro® is the first oral proteasome inhibitor approved by the FDA to be used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma (who have received one prior therapy). The Ninlaro® regimen was found to have a statistically significant improvement in progression free survival as compared to the placebo regimen.

It is recommended that Ninlaro® require clinical prior authorization to verify previous treatment failure and concurrent use of lenalidomide and dexamethasone.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Ninlaro [package insert]. Cambridge, MA: Takeda Pharmaceutical Company; 2015.
[2] FDA News Release. FDA approves Ninlaro, new oral medication to treat multiple myeloma. Website: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473771.htm. Accessed January 2016.

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