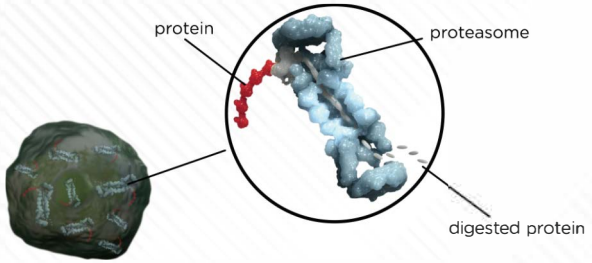
NINLARO™ (ixazomib) Mechanism of Action

NINLARO™
(ixazomib) capsules
4mg | 3mg | 2.3mg

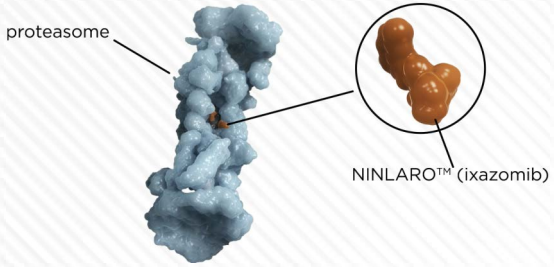
1. MYELOMA CELL

2. PROTEIN HOMEOSTASIS



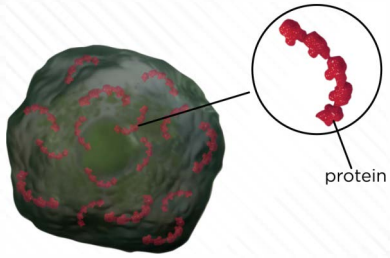
Within the tumor cell, proteasomes break down proteins to maintain a stable cell environment. Because myeloma cells are characterized by excessive production of certain proteins, they are especially dependent upon a functioning proteasome to survive.

3. NINLARO™ (ixazomib)



Takeda's NINLARO™ (ixazomib) temporarily blocks proteasomes from breaking down proteins.

4. PROTEIN BUILDUP



This causes a buildup of proteins in the cell.

5. CELL DEATH

The buildup of proteins can result in cell dysfunction and death.

NINLARO™ (ixazomib): GLOBAL IMPORTANT SAFETY INFORMATION

SPECIAL WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO (28% vs. 14% in the NINLARO and placebo regimens, respectively) with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. It did not result in an increase in hemorrhagic events or platelet transfusions. Monitor platelet counts at least monthly during treatment with NINLARO and consider more frequent monitoring during the first three cycles. Manage with dose modifications and platelet transfusions as per standard medical guidelines.
- **Gastrointestinal Toxicities** have been reported in the NINLARO and placebo regimens respectively, such as diarrhea (42% vs. 36%), constipation (34% vs. 25%), nausea (26% vs. 21%), and vomiting (22% vs. 11%), occasionally requiring use of antiemetic and anti-diarrheal medications, and supportive care.
- **Peripheral Neuropathy** was reported with NINLARO (28% vs. 21% in the NINLARO and placebo regimens, respectively). The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- **Peripheral Edema** was reported with NINLARO (25% vs. 18% in the NINLARO and placebo regimens, respectively). Evaluate patients for underlying causes and provide supportive care, as necessary. Adjust the dose of dexamethasone per its prescribing information or the dose of NINLARO for severe symptoms.
- **Cutaneous Reactions** occurred in 19% of patients in the NINLARO regimen compared to 11% of patients in the placebo regimen. The most common type of rash reported in both regimens was maculo-papular and macular rash. Manage rash with supportive care, dose modification or discontinuation.
- **Hepatotoxicity,** drug-induced liver injury, hepatocellular injury, hepatic steatosis, and hepatitis cholestatic have been uncommonly reported with NINLARO. Monitor hepatic enzymes regularly and adjust dose for Grade 3 or 4 symptoms.
- **Pregnancy -** NINLARO can cause fetal harm. Advise male and females patients of reproductive potential to use contraceptive measures during treatment and for an additional 90 days after the final dose of NINLARO. Women of childbearing potential should avoid becoming pregnant while taking NINLARO due to potential hazard to the fetus. Women using hormonal contraceptives should use an additional barrier method of contraception.
- **Lactation -** It is not known whether NINLARO or its metabolites are excreted in human milk. There could be potential adverse events in nursing infants and therefore breastfeeding should be discontinued.

SPECIAL PATIENT POPULATIONS

- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis. NINLARO is not dialyzable and, therefore, can be administered without regard to the timing of dialysis.

DRUG INTERACTIONS

Co-administration of strong CYP3A inducers with NINLARO is not recommended.

ADVERSE REACTIONS

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen, and greater than in the placebo regimen, were diarrhea (42% vs. 36%), constipation (34% vs. 25%), thrombocytopenia (28% vs. 14%), peripheral neuropathy (28% vs. 21%), nausea (26% vs. 21%), peripheral edema (25% vs. 18%), vomiting (22% vs. 11%), and back pain (21% vs. 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

For US Prescribing Information: https://www.ninlarohcp.com/pdf/prescribing-information.pdf

For Canada Product Monograph: http://www.takedacanada.com/ninlaropm

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