Ixazomib Fact Sheet

(ix-AZ-oh-mib)

Generic Name: Ixazomib

Trade Name: Ninlaro® from Takeda

Drug Type: Ixazomib is a targeted therapy and is classified as a "proteasome inhibitor." (For more detail, see "**How Does Ixazomib Work?**" below)

What Conditions Are Treated by Ixazomib?
Ixazomib has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of relapsed/refractory multiple myeloma. It is a newer proteasome inhibitor that is administered orally. It has been evaluated in clinical trials for the treatment of Waldenstrom macroglobulinemia (WM). Like most of the therapies used to treat WM (except ibrutinib and zanubrutinib), ixazomib has not been approved by the FDA for the treatment of WM and as such, its usage is considered “off label.” Off label use means that if a drug has been approved for one use, physicians may elect to use this same drug for other conditions or in different combinations if they believe it may be helpful. The rationale for using ixazomib in WM is that the proteasome inhibitors, bortezomib (Velcade) and carfilzomib (Kyprolis) have been shown to have high efficacy in WM but with high rates of peripheral neuropathy (numbness/tingling of the hands/feet) with bortezomib and an increased risk of cardiac events with carfilzomib. Ixazomib is well-tolerated, has high efficacy, and it has lower rates of peripheral neuropathy and cardiovascular events.

How Does Ixazomib Work?
Proteasome inhibition is a standard of care for the treatment of patients with WM, with an approximate rate of use as a first-line therapy in 10% to 15% of patients with WM, reported in a United States Surveillance, Epidemiology, and End Results–Medicare database population-based study. Similarly, a large registry study from Europe reported an approximate rate of use of 5% to 10% of proteasome inhibitors in the treatment of patients with WM. Several studies have reported encouraging results on the combination of proteasome inhibitors and rituximab as primary therapy in patients with WM, with overall response rates between 85-95%, major response rates between 60-80%, and median progression free survival between 40-60 months. However, treatment discontinuation has been reported due to peripheral neuropathy with bortezomib and due to cardiac events with carfilzomib, especially in patients over 65 years of age. In addition, bortezomib is administered intravenously or subcutaneously and carfilzomib is administered intravenously, requiring once or twice weekly visits to infusion centers for treatment, whereas ixazomib can be taken at home.

Ixazomib targets and reversibly inhibits the proteasome enzyme complex within the cell. The proteasome is part of the cell machinery that degrades and disposes of unnecessary or defective proteins, like a garbage disposal. When inhibitory drugs such as ixazomib disrupt the proteasome, protein “garbage” accumulates and clogs the cell, leading to cell death (apoptosis). Some types of cancer cells, such as those in WM, make and accumulate proteins more quickly and are therefore more susceptible to the action of proteasome inhibitors than normal cells.

Ixazomib combined with dexamethasone and rituximab (IDR regimen) was evaluated in a Phase 2 clinical trial of 26 previously untreated WM patients. All participants had the MYD88 L265P mutation, and 58% also had a CXCR4 mutation. The overall response rate was 96%, which was unaffected by CXCR4 mutation status. The median time to response was longer in patients with CXCR4 mutations (12 weeks vs. 8 weeks), but there was no statistically significant difference in progression-free survival based on CXCR4 mutation status. The most common adverse events were mild gastrointestinal symptoms and rituximab-related infusion reactions.

IDR was also evaluated in a Phase 2 trial of 59 relapsed/refractory WM patients in The Netherlands, Belgium, and Greece. The first dose of rituximab was intravenous, with subsequent doses administered subcutaneously. The overall response rate was 71%. Serious adverse events occurred in 16 patients and were mainly infections. There was new onset or worsening of peripheral neuropathy in 16 patients (grade 1 in 69%; grade 2 in 25%) and it was reversible in 10 of the 16 patients. In this study, there was no statistically significant difference in progression-free survival based on CXCR4 mutation status, although there was a tendency for the patients with CXCR4 mutations to have shorter progression-free survival.

This Fact Sheet is based on the National Comprehensive Cancer Network (NCCN® Guidelines) and the most recent consensus treatment recommendations from the International Workshop for Waldenstrom macroglobulinemia (IWWM). The NCCN® is a non-profit alliance of 31 cancer centers in the United States. The IWWM is a bi-annual workshop for the WM scientific community to collaborate and share their latest research. IDR is not a preferred regimen for first-line use in the National Comprehensive Cancer Network (NCCN® Guidelines) and the International Workshop for Waldenstrom macroglobulinemia (IWWM), but it is an alternate option in the first-line setting. As is true with other proteasome inhibitors, prophylaxis for shingles is strongly recommended, and reduction in IgA and IgG levels can occur.

How Is Ixazomib Given?

Ixazomib is given by mouth as a 4 mg capsule once a week for three out of four weeks (Days 1, 8, 15 of a 28-day cycle), accompanied by dexamethasone on the same days and by intravenous rituximab on day 1 starting at Cycle 3. Rituximab is typically not given during Cycles 1 and 2 due to the risk of IgM flare. This protocol is administered for six 4-week induction cycles followed by six 8-week maintenance cycles, for a total of 12 cycles.

The capsule should be taken on an empty stomach (one hour before or two hours after a meal), and it should be swallowed whole with a glass of water. The capsule cannot be crushed, chewed, or dissolved. Ixazomib should be taken on the same day of the week and at the same time of day. If a dose is delayed or missed, it should be taken only if the next scheduled dose is at least 72 hours away. If vomiting occurs, the dose should not be repeated but resumed at the next scheduled dose. The amount of ixazomib that is prescribed depends on many factors, including general health or other health problems (e.g., kidney, liver problems). Your health care team will determine the exact dosage and schedule.

Shingles (herpes zoster) prevention is achieved via antiviral medications. Proton pump inhibitors or H2 blockers to block and decrease the production of stomach acids are administered throughout IDR therapy. Precautionary use of plasmapheresis before the administration of rituximab is recommended for patients with serum IgM levels of 4000 mg/dL or more to minimize the risk of IgM flare (very high levels of IgM).

What Are the Side Effects of Ixazomib?

The side effects of ixazomib and their severity depend on how much of the drug is given. High doses may produce more severe side effects. Most people will not experience all the side effects listed in this fact sheet. Side effects are often predictable in terms of their onset, duration, and severity. They are almost always reversible and will go away after therapy is completed. Ixazomib side effects may be quite manageable. There are many options to minimize or prevent the side effects of ixazomib.

The following ixazomib side effects are common and temporary (occurring in greater than 30% of patients): low blood counts (red cells, white cells, and platelets) that increase the risk for blood transfusion, infection, and/or bleeding. Platelets are lowest between days 14-21 of the 28-day cycle. Diarrhea and/or constipation are also common side effects.

The following less common side effects (occurring in 10-29% of patients) include: peripheral neuropathy (numbness/tingling of your hands/feet), nausea, eye disease (blurred vision, dry eye, and conjunctivitis)., peripheral edema (swelling of the lower legs/ankles), vomiting, skin rash, and upper respiratory infection.

Not all side effects are listed above. Side effects that are very rare -- occurring in less than about 10 percent of patients -- are not listed here. But you should always inform your health care provider if you experience any unusual symptoms.

When Should a Health Care Provider Be Contacted?
Contact your health care provider immediately, day or night, if you should experience any of the following symptoms**:**

- Fever of 100.4º F (38º C) or higher, chills (possible signs of infection)
- Unusual bleeding or bruising
- Black or tarry stools, or blood in your stools
- Blood in the urine

The following symptoms require medical attention but are not an emergency. Contact your health care provider within 24 hours of noticing any of the following:

- Nausea (interferes with ability to eat and unrelieved with prescribed medication)
- Vomiting (vomiting more than 4-5 times in a 24-hour period)
- Diarrhea (4-6 episodes in a 24-hour period)
- Constipation unrelieved by laxative use
- Extreme fatigue (unable to carry on self-care activities)
- Mouth sores (painful redness, swelling, and ulcers)
- Yellowing of the skin or eyes
- Swelling of the feet or ankles
- Sudden weight gain
- Signs of infection such as redness or swelling, pain on swallowing, coughing up mucous, or painful urination
- Unable to eat or drink for 24 hours or have signs of dehydration: tiredness, thirst, dry mouth, dark and decreased amount of urine, or dizziness

Always inform your health care team if you experience any unusual symptoms.

What Are Some Self-Care Tips While Taking Ixazomib?

- Drink at least two to three quarts of fluid every 24 hours, unless instructed otherwise.
- Due to increased risk of infection, try to avoid crowds or people with colds and report fever or any other signs of infection immediately to your health care team.
- Wash your hands often.
- To help treat/prevent mouth sores, use a soft toothbrush, and if you should have mouth sores/discomfort, rinse three times a day with 1 teaspoon of baking soda with 8 ounces of water.
- Use an electric razor and a soft toothbrush to minimize bleeding.
- Avoid contact sports or activities that could cause injury.
- To reduce nausea, take anti-nausea medication as prescribed by your health care team and eat small, frequent meals.
- Follow regimen of anti-diarrhea medication as prescribed by your health care team.
- If diarrhea occurs, diet changes may help reduce diarrhea:
    - Drink plenty of clear fluids (8-10 glasses per day). Examples: Gatorade®, broth, Jello®, water, etc.

  - Eat small amounts of soft bland low fiber foods frequently. Examples: banana, rice, noodles, white bread, skinned chicken, turkey, or mild white fish.
  - Avoid foods such as:
    - Greasy, fatty, or fried foods.
    - Raw vegetables or fruits.
    - Strong spices.
    - Whole grains breads and cereals, nuts, and popcorn.
    - Gas forming foods & beverages (beans, cabbage, carbonated beverages).
    - Lactose-containing products, supplements, or alcohol.
    - Limit foods and beverages with caffeine and beverages that are extremely hot or cold.
- To keep the bowels moving if constipation develops, your health care team may prescribe a stool softener to help prevent constipation that may be caused by this medicine.
- Avoid sun exposure. Wear SPF 30 (or higher) sunblock and protective clothing.
- In general, drinking alcoholic beverages should be kept to a minimum or avoided completely. This should be discussed with your health care team.
- Get plenty of rest.
- Maintain good nutrition.
- Remain active as able. Gentle exercise is encouraged, such as a daily walk.
- Before starting ixazomib treatment, make sure you tell your doctor about *any* other medications you are taking (including prescription, over-the-counter, vitamins, herbal remedies, etc.) There may be serious drug interactions.
- Do not take aspirin or products containing aspirin unless your doctor specifically permits this.
- Do not take St. John's Wort while you are on this therapy.
- Do not receive any kind of immunization or vaccination without your doctor's approval while taking ixazomib.
- Inform your health care professional if you are pregnant or may be pregnant prior to starting this treatment. Ixazomib may cause fetal harm when given to a pregnant woman thus the drug must not be given to a pregnant woman or a woman who intends to become pregnant. If a woman becomes pregnant while taking ixazomib, the medication must be stopped immediately, and the woman given appropriate counseling.
- For both men and women: Use contraceptives and do not conceive a child (get pregnant) while taking ixazomib. Barrier methods of contraception, such as condoms, are recommended for 90 days after the last dose of ixazomib.
- Do not breast feed while taking ixazomib.
- If symptoms or side effects are experienced, be sure to discuss them with your health care team. They can prescribe medications and/or offer other suggestions that are effective in managing such problems.

How is Monitoring and Testing Done While Taking Ixazomib?

You will be checked regularly by your health care team while you are taking ixazomib, to monitor side effects and to check your response to therapy. Periodic blood work will be ordered to monitor your complete blood count (CBC) as well as the function of other organs (such as your kidneys and liver).

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About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer- led, nonprofit 501(c)(3) organization with an important vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM while advancing the search for a cure."

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.