Understanding NINLARO®
(ixazomib) capsules

A publication of the **International Myeloma Foundation**

INTERNATIONAL
MYELOMA
FOUNDATION

12650 Riverside Drive, Suite 206
North Hollywood, CA 91607 USA

Telephone:

800.452.CURE
(USA & Canada)

818.487.7455
(worldwide)

Fax: **818.487.7454**

TheIMF@myeloma.org

myeloma.org

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Improving Lives **Finding the Cure**®

INTERNATIONAL MYELOMA FOUNDATION

Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.

RESEARCH The signature project of the IMF's Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF's International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF's Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

EDUCATION The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF's library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

SUPPORT The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

ADVOCACY The IMF's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.
Contact us at 818.487.7455 or 800.452.CURE,
or visit myeloma.org.

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What you will learn from this booklet

The IMF's *Understanding* series of booklets is designed to acquaint you with treatments and supportive care measures for **multiple myeloma** (which we refer to simply as "myeloma"). Words in **bold+blue** type are explained in the "Terms and definitions" section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF's *Glossary of Myeloma Terms and Definitions*, located at glossary.myeloma.org.

Myeloma is a **cancer** that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful that discussion will be.

This booklet discusses Ninlaro® (also known by its **generic drug name**, ixazomib), an oral medication taken in capsule form rather than an **intravenous (IV)** drug that is administered at a clinic or doctor's office. Because Ninlaro is taken as a pill, the responsibility for taking this medication as directed by your doctor falls on you, the patient. It is crucial that you read and understand the information in this booklet and in any other materials that your healthcare team provides to you.

Ninlaro is approved by the US Food and Drug Administration (FDA) for use in myeloma combination with the **immunomodulatory drug** Revlimid® (lenalidomide) and the **corticosteroid** dexamethasone. Therefore, there are three additional IMF publications that are helpful companions to this booklet. We recommend that you read the following:

- *Understanding Adherence to Oral Cancer Therapy*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding REVLIMID® (lenalidomide)*

All IMF publications are free of charge and can be viewed, downloaded, or ordered at publications.myeloma.org

What is Ninlaro?

Ninlaro is an oral medication to treat myeloma. It is the first oral **proteasome inhibitor** approved by the FDA to treat myeloma. Proteasome inhibitors are a class of drugs. Proteasome inhibitors have been approved as an effective method of treating myeloma since 2003. Ninlaro is the third proteasome inhibitor approved for the treatment of myeloma.

How does Ninlaro work?

Proteasomes, enzyme complexes found in the nucleus of every cell in the body, including cancer cells, are often likened to protein garbage disposers. Proteasomes break down, or degrade, unneeded or damaged proteins into smaller components. Proteasomes also carry out the regulated breakdown of undamaged proteins in the cell, a process that is necessary for the control of many critical cellular functions. These smaller components of degraded proteins are used to create new proteins required by the cell. Proteasomes can thus be thought of as crucial to the cell's "recycling" of proteins.

If the proteasome is stopped, or inhibited, then the damaged and unneeded cellular proteins build up in the cell's **nucleus** and **cytoplasm** and cause it to die. Myeloma cells are particularly sensitive to proteasome inhibition (more so than healthy cells), so proteasome inhibitors are effective treatments for myeloma.

What is the indication for use of Ninlaro?

Ninlaro is indicated in combination with Revlimid® (generic name lenalidomide) and dexamethasone for patients with myeloma who have received at least one prior therapy. In November 2015, Ninlaro was approved by the FDA for this indication based on the results of a large, phase III randomized **clinical trial**. Ninlaro was approved for the same indication by the European Commission in November 2016, becoming the first and only oral proteasome inhibitor approved for use across the European Economic Area, which includes the 28 member states of the European Union (EU) plus Norway, Liechtenstein, and Iceland.

What is the clinical trial experience with Ninlaro?

Ninlaro was approved by the FDA and the European Commission based upon the data from the TOURMALINE study, an international phase III clinical trial of Ninlaro + Revlimid + dexamethasone versus **placebo** + Revlimid + dexamethasone in 722 patients with **relapsed** and/or

refractory myeloma who had received at least one prior line of therapy. Patients whose myeloma did not respond to prior treatment with Revlimid or proteasome inhibitors were not eligible to participate in the study. Patients in both the experimental arm (which included Ninlaro) and the control arm (which substituted a placebo for Ninlaro) were treated until their myeloma progressed or they were unable to tolerate the treatment.

The efficacy of Ninlaro was evaluated by the **median** duration of **progression-free survival (PFS)** in the two arms of the study. Updated PFS data from the TOURMALINE study were published in November, 2017. The median PFS was improved with Ninlaro + Revlimid + dexamethasone versus placebo + Revlimid + dexamethasone in both high-risk and standard-risk subgroups. High-risk patients are defined as those whose myeloma cells carry the del(17p), t(4;14), and/or t(14;16) genetic mutations. High-risk patients in the Ninlaro arm of the study had median PFS of 21.4 months; high-risk patients in the placebo arm had median PFS of 9.7 months. Standard-risk patients had median PFS of 20.6 months with Ninlaro versus 15.6 months without Ninlaro. The median time of **response** to therapy was 1.1 months for the Ninlaro regimen and 1.9 months for the regimen using a placebo. The **overall response rate (ORR)** was 78% in the Ninlaro arm and 72% in the placebo arm.

Patients in the study were given a blood thinner to prevent blood clots, as recommended for all patients taking Revlimid and dexamethasone. Other medications were given as necessary at the physicians' discretion to improve patients' tolerance of the drugs. For more information on recommended medications, please read the section of this booklet on Supportive Care.

Ninlaro is being studied in clinical trials in a wide spectrum of combination therapies and across disease settings. The following clinical trial results indicate its potential new applications:

- In July 2018, the phase III TOURMALINE-MM3 clinical trial of single-agent Ninlaro used as a maintenance therapy after autologous stem cell transplant, met its primary endpoint and resulted in a statistically significant increase in PFS compared to placebo. Data from the clinical trial have been submitted to regulatory agencies around the world, including the FDA in the United States, to evaluate approval of Ninlaro in the maintenance setting.
- Also in July 2018, results of a phase I/II clinical trial of Ninlaro + melphalan + prednisone induction treatment followed by weekly single-agent Ninlaro maintenance in transplant-ineligible newly diagnosed myeloma patients revealed that after a median of 43.6 months of follow-up, almost half of the patients achieved a CR or VGPR, with an ORR of 66%. Maintenance therapy showed a deepening of responses in about one third of patients.
- In October 2018, results of a phase I/II clinical trial of Ninlaro + cyclophosphamide + dexamethasone for newly diagnosed, previously untreated myeloma were published in the journal *Blood*. Patients received Ninlaro once weekly, and could remain on Ninlaro after the mandated 12 cycles of therapy until disease progression, withdrawal from the study, or unacceptable toxicity. The ORR rate was 78%, with 38% of patients achieved at least a VGPR. Median PFS and OS were not yet reached.

Visit matrix.myeloma.org for more information about these and other clinical trials listed in the IMF's *Myeloma Matrix 2.0: Smart Search*.

What are the dose and schedule of Ninlaro + Revlimid + dexamethasone?

Ninlaro is taken in 4-week (28-day) cycles. The recommended starting dose of Ninlaro is one 4 mg capsule taken orally on Days 1, 8, and 15 of a 28-day treatment cycle. Thus, one capsule of Ninlaro is taken once a week for the first three weeks of every 4-week (28-day) cycle. No Ninlaro is taken during the fourth week of each cycle.

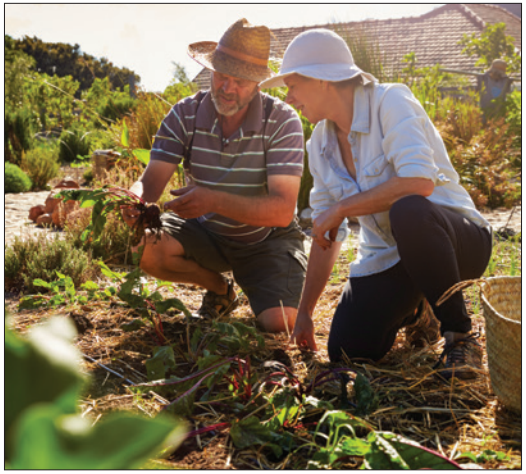
Ninlaro also comes in 3 mg and 2.3 mg capsules, and your doctor can reduce the dose of Ninlaro depending upon your medical status and side effects. If you have moderate or severe liver or kidney dysfunction at the time you start treatment with Ninlaro, your dose of Ninlaro should be lowered. The starting dose for patients with moderate to severe liver or kidney impairment is 3 mg. For patients with kidney disease requiring dialysis, Ninlaro is not dialyzable and therefore can be administered without regard to the timing of dialysis.

The recommended starting dose of Revlimid is 25 mg taken orally on Days 1 through 21 of a 28-day treatment cycle.

The recommended starting dose of dexamethasone is 40 mg taken orally on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

If necessary, your doses of Revlimid and dexamethasone can be lowered by your doctor.

Be sure to report any new health-related problems you're having to a member of your healthcare team.



Important instructions for taking Ninlaro safely

Read these safety instructions carefully BEFORE you take Ninlaro:

- Take the Ninlaro + Revlimid + dexamethasone combination therapy exactly as your healthcare provider instructs.
- Take Ninlaro on the same day each week. This is important for efficacy and safety, and will help you establish a routine for remembering to take your medication.
- Take Ninlaro at about the same time of day each week.
- Take Ninlaro at least 1 hour before, or at least 2 hours after, eating (i.e., on an empty stomach).
- DO NOT take Ninlaro at the same time you take dexamethasone, because dexamethasone should be taken with food, and Ninlaro should not be taken with food.
- Store Ninlaro capsules at room temperature in their original packaging. Do not remove the capsule from the packaging until just before you take it.
- Swallow the whole Ninlaro capsule with a full glass of water.
- Do not crush, chew, or open the Ninlaro capsule.
- Avoid direct contact with the contents of the Ninlaro capsule. If you accidentally get powder from inside the capsule on your skin, wash the area well with soap and water. If you get it in your eyes, flush your eyes well with water.
- If you miss or delay a dose of Ninlaro, take the dose as long as the next scheduled dose is more than 3 days (72 hours) away. DO NOT take a missed dose of Ninlaro if it is within 3 days (72 hours) of your next scheduled dose.
- If you vomit after taking a dose of Ninlaro, DO NOT repeat the dose. Just take your next dose of Ninlaro on the next scheduled day at the usual time.
- If you take more Ninlaro than your healthcare provider has prescribed, call your provider immediately or go to the nearest hospital emergency room.
- Tell your doctor about all other medications and supplements that you're taking before you take your first dose of Ninlaro.
- Tell your doctor about all of your medical conditions. Special precautions must be taken with your dosing if you have liver or kidney problems or diabetes.
- Tell your doctor if you are pregnant or plan to become pregnant. You should not become pregnant while taking Ninlaro, which can harm your unborn baby.
- Tell your doctor if you are breastfeeding or plan to breastfeed while taking Ninlaro. You should not breastfeed while taking Ninlaro.

What are the possible side effects, and how are they managed?

Careful records of all drug-related and possibly drug-related side effects are maintained during clinical trials. All the side effects experienced by patients in both arms of the TOURMALINE clinical trial were recorded for evaluation prior to the approval of Ninlaro in combination with Revlimid and dexamethasone. The below side effects occurred most commonly among the patients enrolled in the TOURMALINE clinical trial, but other, less common side effects occurred as well. In addition, serious side effects outside of clinical trials have been reported to the regulatory agencies. If you are a patient in the US, you and/or your doctor should report side effects to the FDA at fda.gov or by calling 800.332.1088.

In addition to the most common side effects listed below, back pain is also common while taking Ninlaro. You should promptly report any changes in your health to your healthcare providers while you are taking Ninlaro + Revlimid + dexamethasone. Some side effects can be life-threatening if not managed promptly and effectively.

Thrombocytopenia (low platelet count)

Thrombocytopenia is a lowered level of platelets in the blood. Platelets help blood to clot; fewer platelets can lead to bruising, bleeding, and slower healing. Both Ninlaro and Revlimid can cause platelet counts to drop. During treatment with Ninlaro + Revlimid + dexamethasone, the platelet count reaches its lowest point on days 14–21 of each 28-day cycle, but usually recovers to baseline by the beginning of the next cycle. That is why there is no Ninlaro dose during week four of each cycle. 78% of the patients in the Ninlaro arm of the TOURMALINE clinical trial and 54% of the patients in the placebo arm had thrombocytopenia, some of it severe enough to be life-threatening.

Prevention and treatment of thrombocytopenia

Your doctor should monitor your complete blood count (CBC) throughout your treatment with Ninlaro + Revlimid + dexamethasone. You should inform the members of your healthcare team if you experience excessive bruising or bleeding. Management of thrombocytopenia may include holding your Ninlaro and Revlimid treatment until your platelet count recovers and then lowering your Ninlaro and Revlimid doses. Some patients with persistent low platelet counts may require platelet transfusions.

Diarrhea

In the TOURMALINE clinical trial, 42% of the patients in the Ninlaro + Revlimid + dexamethasone arm and 36% in the placebo arm (Revlimid + dexamethasone without Ninlaro) experienced diarrhea. While no patient in the study had diarrhea that was life-threatening, 6% of the cases in the Ninlaro arm and 2% of the cases in the placebo arm were severe.

Prevention and treatment of diarrhea

Antidiarrheal medications such as Imodium® (loperamide) can help control diarrhea. If you have diarrhea, take precautions to prevent dehydration by drinking a sufficient amount of water, and call the doctor's office or clinic where you're being treated. Your doctor should monitor your **electrolytes** (potassium, in particular) and correct electrolyte abnormalities if they're detected. Call for immediate medical advice if you experience dizziness, light-headedness, or fainting. Your physician may hold or reduce your Ninlaro and Revlimid doses or administer antidiarrheal medication or intravenous hydration, as required.

Constipation

Prevention is the key to managing constipation, which is defined as having fewer than three bowel movements a week. Chronic constipation is defined as infrequent bowel movements or difficult passage of stools that persists for several weeks or longer.

While 34% of the patients in the Ninlaro arm and 25% in the placebo arm of the TOURMALINE clinical trial experienced constipation, less than 1% of cases in either arm were considered serious. Sometimes constipation is the flip side of diarrhea, with patients cycling back and forth between these two uncomfortable states. Talk to your healthcare providers about strategies to regulate your bowel health.

Prevention and treatment of constipation

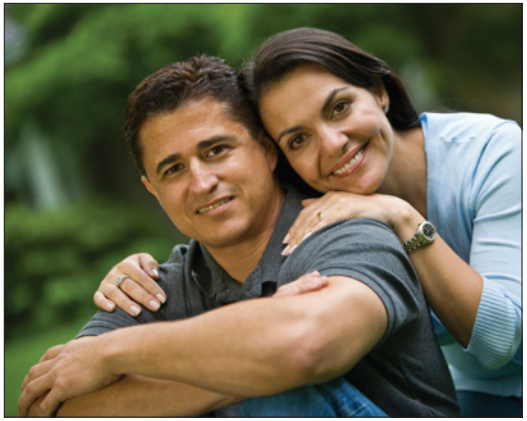
There are several strategies that may help alleviate constipation:

- Drink at least eight 8-ounce glasses of fluid daily.
- Add plenty of dietary fiber every morning, such as prune juice, apple juice, or bran.
- Get some exercise daily, even if it's just walking. Moving your body increases peristalsis, the rhythmic contractions that move food through the digestive system.
- Report the problem to a member of your healthcare team, who may recommend a stool softener or laxative.

Nausea and vomiting

Nausea affected 26% and 21% of the patients in the Ninlaro and placebo arms of the TOURMALINE clinical trial, respectively, and vomiting occurred in 22% and 11%, respectively. None of these episodes was life-threatening.

Prevention and treatment of nausea



You should be premedicated with drugs to help prevent nausea and vomiting prior to each dose of Ninlaro. Precautions should be taken to prevent dehydration caused by vomiting. You should drink a sufficient amount of water and other fluids and seek medical advice if you experience dizziness, lightheadedness, or fainting. Your physician may administer anti-emetic medication (to prevent vomiting) or intravenous hydration, as required.

Peripheral neuropathy

Peripheral neuropathy (PN) is a serious condition in which treatment affects nerves in the hands, feet, legs, and/or arms. Symptoms of PN include numbness, tingling, cramping, burning, weakness, or pain in the hands, feet, legs, and/or arms. Some patients may have experienced PN from the effects of the myeloma itself and/or from previous treatments for myeloma. If you begin taking Ninlaro with peripheral neuropathy as a pre-existing condition, it is especially important that you pay attention to any increase in your discomfort. Report a worsening of your condition to your doctor immediately. If detected and managed appropriately, your neuropathy should not become worse. If these signs and symptoms are new to you, dealing with them promptly may prevent them from becoming a long-term problem.

28% of the patients on the Ninlaro arm of the TOURMALINE study reported PN; 18% of it was mild enough not to cause pain or affect the activities of daily living (grade 1 on a scale of 1–4). In the Revlimid + dexamethasone + placebo arm, 21% reported PN, of which 14% was grade 1. Only 2% of patients in either arm of the study reported PN that caused severe pain, weakness, or numbness that interfered with the activities of daily living.

Prevention and treatment of peripheral neuropathy

The best approach to treating PN is to prevent it from occurring or worsening. By promptly reporting any signs of numbness or tingling to your doctor, you can avoid potentially painful or disabling neuropathy.

Your doctor will withhold or lower the dose of Ninlaro and Revlimid until your symptoms improve. If you develop more serious neuropathy, the doctor may prescribe a medication to help, may refer you to a neurologist or a physical therapist, and/or may discontinue your treatment regimen.

Peripheral edema

Peripheral edema is accumulation of fluid that causes swelling, usually in the ankles, feet, and legs. This swelling is the result of the accumulation of excess fluid under the skin in the spaces within the tissues, or "interstitial" spaces. Peripheral edema can be a side effect of long-term use of anti-inflammatory medications (such as the corticosteroid dexamethasone), which increase fluid pressure from sodium and water retention, and thereby upset the balance of inflow and drainage of interstitial fluid. Peripheral edema can also result from many other causes, including immobility, obesity, varicose veins, cardiac, kidney, or liver dysfunction, gastrointestinal disorders, medications for diabetes such as insulin and pioglitazone, and non-steroidal anti-inflammatories such as ibuprofen and naproxen. Usually peripheral edema affects both legs/ankles/feet. If you have swelling in one leg only, you should tell your healthcare team immediately, as it might signal the presence of a blood clot.

Peripheral edema affected 25% and 18% of patients in the Ninlaro and placebo regimens of the TOURMALINE clinical trial, respectively. The majority of the cases of peripheral edema were mild and none were life-threatening.

Prevention and treatment of peripheral edema

Patients should be evaluated for underlying causes of peripheral edema and provided supportive care, as necessary. A reduction in dietary salt intake may be required. The dose of dexamethasone may be modified, and if the edema is severe, the dose of Ninlaro should also be adjusted.

Rash

Rash was reported in 19% of patients in the Ninlaro regimen and 11% of the patients in the placebo regimen in the

TOURMALINE clinical trial. The majority of these cases were mild, and fewer than 1% of the patients in either arm discontinued one or more of the three drugs because of a skin reaction. However, rash can be a serious concern. It is potentially dangerous, as a rash may be mild initially and then escalate in severity. Drug rashes vary in severity from mild redness with tiny bumps over a small area to peeling of the entire skin. Rashes may appear suddenly within minutes after a person takes a drug, or they may be delayed for hours or days.

Prevention and treatment of rash

Notify your doctor right away if you experience a rash. Proper evaluation of a skin rash requires a visit to a doctor or other healthcare professional. If detected and managed appropriately, a rash is reversible. The dose of Revlimid should be held until the rash recovers, and then Revlimid should be given at a lower dose. If the rash appears again, the doses of both Ninlaro and Revlimid should be modified. For a life-threatening rash, the treatment regimen should be discontinued altogether.

Liver toxicity (hepatotoxicity)

Drug-induced liver injury was reported in 6% of patients treated with Ninlaro and 5% of the patients treated with placebo in the TOURMALINE study. Signs of liver toxicity include yellowing of your skin or the whites of your eyes and/or pain in your right upper-stomach area.

Prevention and treatment of hepatotoxicity

Your doctor will monitor your liver enzymes with regular blood tests while you are being treated with Ninlaro + Revlimid + dexamethasone. If you have moderate to severe liver impairment, your dose of Ninlaro should be reduced.

Eye disorders

Eye disorders of different types were reported in 26% of the patients in the Ninlaro regimen and 16% of the patients in the placebo regimen of the TOURMALINE clinical trial. The most common disorders were blurred vision, dry eye, and conjunctivitis (pinkeye), an inflammation of the thin, clear tissue that lies over the white part of the eye. 2% of the patients in the Ninlaro arm and 1% of the patients in the placebo arm had more serious eye side effects.

Prevention and treatment of eye disorders

Eye disorders are readily detectable, so reporting and seeking remedy for them can and should be done as soon as you experience a problem. Members of your healthcare team may provide supportive care or refer you to an eye specialist.

Fetal harm

Based on findings with animals, Ninlaro can cause fetal harm when administered to a pregnant woman. There are no adequate or well-controlled studies in pregnant women, but studies in rats and rabbits that were exposed to the medication at slightly higher levels than those observed in patients caused embryo-fetal toxicity. Women of childbearing potential should not become pregnant while taking Ninlaro. Animal studies indicated that there were no effects due to Ninlaro on male or female reproductive organs.

Prevention of fetal harm

Both male and female patients of childbearing potential should use effective contraceptive measures during treatment with Ninlaro and for 90 days following the final dose.

Supportive care

Patients taking Ninlaro + Revlimid + dexamethasone are at an increased risk for herpes zoster viral infection (shingles), **venous thromboembolic (VTE)** events, and peripheral neuropathy (PN). The IMF's Nurse Leadership Board recommends the following supportive care measures for patients on this regimen:

- All patients should be given preventive treatment with an anti-viral medication to prevent shingles, a reactivation of the herpes zoster virus. All patients taking a proteasome inhibitor are at risk for reactivation of the herpes zoster virus.
- All patients should receive preventive treatment with a blood thinner (anti-coagulant) to prevent a possible VTE.
- Watch for the signs and symptoms of PN listed above so that you can report the onset or worsening of symptoms immediately.
- Get regular physical activity, which will help combat muscle weakness (a possible dexamethasone side effect), prevent blood clots, and improve your mood.

Access to Ninlaro and other resources

Takeda Oncology, the company that developed Ninlaro, has established the website ninlaro.com and the "NINLARO Empower" program. Complete the Empower enrollment form at ninlaro.com/empower or call 844.617.6468 (select option 2) to learn about comprehensive programs that can assist with the financial burden and other day-to-day needs associated with your Ninlaro treatment. "NINLARO Empower" services include the following:

- Helping you understand your insurance coverage for Ninlaro.
- Providing information about specialty pharmacies that supply Ninlaro.
- Assisting eligible patients with out-of-pocket costs.
- Helping you start your medication as quickly as possible, as directed by your doctor.
- Connecting you with additional resources, such as legal services, counseling and support programs, emotional support, and transportation assistance.

Eligible patients could pay as little as $25 per prescription of Ninlaro.

For a list of other organizations that may be able to assist with drug access and reimbursement, please visit resources.myeloma.org.

In closing

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org or 818.487.7455 or 800.452.CURE.

Terms and definitions

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Clinical trial: A research study of new treatment that involves patients. Each study is designed to find better ways to prevent, detect, diagnose, or treat cancer and to answer scientific questions.

- ***Control group*** – The arm of a randomized clinical trial that receives the standard treatment or placebo (no treatment).
- ***Experimental group*** – The arm of a randomized trial that gets the new treatment.
- ***Randomized clinical trial*** – A research study in which subjects are randomly assigned to receive a particular treatment or not.
- ***Arm*** – One of the treatment groups of a randomized trial. The majority of randomized trials have two, but some have more.
- ***End point*** – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.
- ***Double blind*** – Aspect of a randomized trial in which neither the participant nor the investigator knows the arm of the trial to which the patient is assigned. The purpose is to eliminate any bias in the reporting of results.
- ***Phase I trial*** – A trial designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well tested. Patients in phase I trials generally have advanced cancer that is refractory to all standard treatment. In a typical phase I trial, successive groups ("cohorts") of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.
- ***Phase II trial*** – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment. In addition,

patients must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may be approved based on phase II trial results.

- ***Phase III trial*** – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don't choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.
- ***Phase IV trial*** – Even after a drug has been approved by the United States Food and Drug Administration (FDA) for use in a particular indication, there may be need for additional studies. Phase IV clinical trials may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons. For example, safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than was possible during the phase I–III clinical trials.

Corticosteroid: A group of natural and synthetic analogues of the hormones secreted by the pituitary gland. These include the glucocorticoids used in the treatment of myeloma such as dexamethasone, prednisone, and methylprednisolone. Glucocorticoids have multiple effects and are used for a large number of conditions.

Cytoplasm: The jellylike material inside the membrane of a human cell, excluding the cell's nucleus.

Deep vein thrombosis (DVT): A condition that occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body, usually in the legs. DVT can cause leg pain or swelling, but can occur without any symptoms.

Electrolytes: Minerals in your blood and other body fluids that carry an electrical charge and are essential for life. Electrolytes include sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate. They affect the amount of water in the body, the acidity of the blood (pH), nerve and muscle function (including the heart), and other important processes.

Generic drug name: A generic drug name refers to the chemical makeup of a drug rather than its brand name. A generic name is given to a drug before it is approved and given a brand name. After a drug goes off patent, other manufacturers may make generic versions of the drug. For example: ibuprofen is the generic name for drugs brand-named Advil® and Motrin®.

Immunomodulatory drug: An agent that affects, enhances, or suppresses the immune system. Sometimes called an IMiD® compound.

Intravenous (IV): Administered into a vein.

Median: The middle number or the mean of the two central numbers in a series of numbers. For example, "median progression-free survival (PFS)" means that half the patients had remissions that were shorter than the median PFS, and half the patients had remissions that were longer than the median PFS.

Multiple myeloma: A cancer of the bone marrow plasma cells, white blood cells that make antibodies. The cancerous plasma cells are called myeloma cells.

Nucleus: The nucleus of the cell in advanced organisms is the control center of the cell. It serves two functions: it stores all the genetic material (DNA) of the cell, and it coordinates the cell's activities, which include growth, intermediary metabolism, protein synthesis, and reproduction (cell division).

Overall response rate (ORR): The percentage of patients in a clinical trial whose monoclonal protein decreased by at least 50% in response to treatment.

Placebo: An inert (inactive) substance often used in clinical trials for comparison with an experimental drug. No clinical trial for cancer patients in the United States can ethically or legally randomize patients to receive a placebo alone when they require treatment. In the placebo arm of a cancer treatment trial, patients receive treatment with approved therapy *plus* a placebo.

Progression-free survival (PFS): The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to determine how well a new treatment works. Also called PFS. See "**Progressive disease**."

Progressive disease: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of ≥ 25% from lowest confirmed response value in the myeloma protein level and/or new evidence of disease.

Proteasome: A joined group (or complex) of enzymes that destroy damaged or unwanted proteins and undamaged proteins that require degradation in the cell. This turnover or "recycling" of proteins is important to maintain balance within the cell and helps to regulate several functions including cell growth.

Proteasome inhibitor: Any drug that interferes with the normal function of the proteasome, an enzyme complex responsible for breaking down and recycling unwanted proteins in both normal cells and cancer cells.

Pulmonary embolism (PE): A condition that occurs when a blood clot in the vein (deep vein thrombosis, or DVT) breaks loose, travels through the bloodstream, and lodges in a lung, blocking blood flow.

Refractory: Disease that is no longer responsive to standard treatments. Patients with refractory myeloma have had progressive disease either during treatment or within 60 days following treatment. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Relapse: The reappearance of signs and symptoms of a disease after a period of improvement. Patients with relapsed disease have been treated, then developed signs and symptoms of myeloma at least 60 days after treatment ended. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Response or remission: Complete or partial disappearance of the signs and symptoms of cancer. Remission and response are interchangeable terms.

- ***Stringent complete response (sCR)*** – sCR is CR (as defined below) plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
- ***Complete response (CR)*** – For myeloma, CR is negative immunofixation on serum (blood) and urine, and disappearance of any soft tissue plasmacytomas, and ≤ 5% plasma cells in bone marrow. CR is not the same as a cure.
- ***Very good partial response (VGPR)*** – VGPR is less than CR. VGPR is serum M-protein and urine M-protein detectable by immunofixation but not on electrophoresis, or 90% or greater reduction in serum M-protein, plus urine M-protein less than 100 mg per 24 hours.
- ***Partial response (PR)*** – PR is a level of response in which there is at least a 50% reduction in M-protein, and reduction in 24-hour urinary M-protein by at least 90% (or to less than 200 mg per 24 hours).

Smoldering multiple myeloma (SMM): SMM is a higher level of disease than MGUS, but is still not active myeloma with CRAB features indicating organ damage. Patients with standard-risk SMM do not require treatment, but should be observed at regular intervals by a hematologist-oncologist. Patients with high-risk SMM may choose to participate in a clinical trial.

Transplant (transplantation): There are several different types of transplantation.

- ***Peripheral blood stem cell (PBSC) transplant*** – Doctors remove healthy blood-making stem cells from a patient's circulating blood (not from the bone marrow), which are then frozen and stored. The patient receives high-dose chemotherapy to destroy the cancer cells, but healthy blood cells are also destroyed. The frozen stem cells are then defrosted and returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment.
- ***Autologous transplant*** – A procedure in which stem cells are removed from a patient's blood and then are given back to the patient following intensive treatment.
- ***Bone marrow transplant*** – This term refers to the process of collecting stem cells from the bone marrow and infusing them into a patient. This term is used less frequently today in myeloma as stem cells are now collected from the peripheral (circulating) blood.
- ***Allogeneic (allograft) transplant*** – The infusion of bone marrow or stem cells from one individual (donor) to another (recipient). A patient receives bone marrow or stem cells from a compatible, though not genetically identical, donor. An HLA blood test is done to determine if a patient has a potential donor match. A donor may be a family member or may be obtained through a donor registry such as the National Marrow Donor Program (NMDP). Rarely, donor cells may be obtained from an umbilical cord blood bank. The donor's immune system cells recognize the recipient's myeloma cells as foreign, and attack them. Unfortunately, the donated cells also attack other tissues in the recipient's body, causing graft-versus-host disease (GVHD), which may be fatal.
- ***Reduced-intensity conditioning (RIC) allo transplant*** – A newer and, for myeloma, safer technique than an allogeneic transplant. RIC is a non-myeloablative, reduced-intensity "mini-allo" transplant performed within 180 days after a standard autologous transplant.
- ***Tandem transplant*** – A term used to indicate two autologous transplants done in succession. Tandem transplants are usually planned with 3-month to 6-month intervals between transplants. Tandem transplantation has become less common in the US in the era of effective novel therapies.

- ***Matched unrelated donor (MUD) transplant*** – Refers to a stem cell transplantation procedure in which the patient and the stem cells are genetically matched but are not from family members. This procedure is not recommended for myeloma patients because it carries an unacceptably high mortality rate from graft-versus-host disease (GVHD).
- ***Syngeneic transplant*** – The infusion of bone marrow or stem cells from one identical twin into another.
- ***Umbilical cord blood transplant*** – Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks. Because multiple cords are needed to provide enough stem cells for an adult transplant, the risk of graft-versus-host disease is increased with this type of transplant, making it even riskier for myeloma patients.

Venous thromboembolism (VTE): A condition that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Risk factors include infection, age > 75, cancer, and a history of VTE. See "**Deep vein thrombosis (DVT)**" and "**Pulmonary embolism (PE)**."

Notes

INTERNATIONAL MYELOMA FOUNDATION

You are not alone. The IMF is here to help.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments.

The IMF produces and maintains a library of publications to help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The following is a partial list of publications available in English, and selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding DARZALEX® (daratumumab)*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding Fatigue*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib)*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding POMALYST® (pomalidomide)*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib)*
- *Understanding Your Test Results*

All IMF publications and periodicals are always free of charge. Visit **publications.myeloma.org** to read, download, or order printed copies. Subscribe to IMF periodicals at **subscribe.myeloma.org** or by contacting the IMF.

As always, the IMF urges you to discuss all medical issues with your doctor, and to contact the IMF's InfoLine specialists with your myeloma questions and concerns.

818.487.7455 **800.452.CURE** **TheIMF@myeloma.org**