Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is to be supplied by physician's prescription only

Ninlaro® 2.3 mg
Ninlaro® 3 mg
Ninlaro® 4 mg
Capsules

Active ingredient:

Each capsule of Ninlaro® 2.3 mg contains 2.3 mg of ixazomib (equivalent to 3.3 mg of ixazomib citrate).
Each capsule of Ninlaro® 3 mg contains 3 mg of ixazomib (equivalent to 4.3 mg of ixazomib citrate).
Each capsule of Ninlaro® 4 mg contains 4 mg of ixazomib (equivalent to 5.7 mg of ixazomib citrate).

Inactive ingredients and allergens: See section 6 "Additional information".

Read the entire leaflet carefully before using this medicine. This leaflet contains a summary of the information about this medicine. If you have further questions, refer to the physician or pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar.

This medicine is intended for adults.

1. What is this medicine used for?

Ninlaro in combination with lenalidomide and dexamethasone, is indicated for the treatment of patients with multiple myeloma (a type of cancer of the bone marrow) who have received at least one prior therapy.

Therapeutic group: Antineoplastic agent of proteasome inhibitor class.

2. Before using this medicine

Do not use this medicine if:
You are sensitive (allergic) to the active ingredient or to any other ingredients that this medicine contains (see section 6: "Additional information").

Special warnings regarding the use of this medicine

Before the treatment with Ninlaro, tell your physician about your medical condition, including if:

- you suffer from liver problems
- you suffer from kidney problems or are on dialysis
- you are pregnant or plan to become pregnant (see additional details in Pregnancy and breastfeeding section)
- you are breastfeeding or plan to breastfeed (see additional details in Pregnancy and breastfeeding section)

Laboratory tests and follow-up

During the period of treatment with the medicine, the physician will refer you to perform blood tests in order to monitor side effects.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medications and nutritional supplements, inform your physician or pharmacist.

Tell your physician or pharmacist before starting any new medicines during treatment with Ninlaro.

In particular inform the physician or pharmacist if you are taking medicines belonging to a group of medicines called "strong CYP3A inducers" (such as rifampin, phenytoin, carbamazepine and hypericum (St. John's Wort)).

Using the medicine and food

- **Take Ninlaro at least one hour before or at least two hours after food.**
- **During days on which you are taking Ninlaro and dexamethasone, do not** take both medications at the same time. **Take dexamethasone with food.**

Pregnancy and breastfeeding

- Ninlaro can harm your unborn baby.
    - Avoid becoming pregnant during treatment with Ninlaro.
    - Both men and women of childbearing potential must use effective contraceptives during the treatment with Ninlaro and for 3 months (90 days) following the end of treatment. If using hormonal contraceptives (for example, the pill), an additional barrier method of contraception (for example, diaphragm or condom) must be used.
    - Consult your physician about contraceptives that may be right for you.
    - Immediately notify the attending physician in case of pregnancy if one of the partners is treated with Ninlaro.
- It is not known whether Ninlaro is excreted in breast milk or if it affects an infant who is breastfed or breast milk production. Do not breastfeed during treatment with Ninlaro and for 3 months (90 days) following the end of treatment.

3. How should you use the medicine?

Always use the medicine according to the physician's instructions. You should check with the physician or pharmacist if you are not sure regarding the dosage and the manner of treatment. The dosage and manner of treatment will be determined by the physician only.

Ninlaro is taken in treatment cycles. Each cycle lasts 4 weeks (28 days).

The recommended dose is usually:

One Ninlaro 4 mg capsule once a week on the same day and at about the same time of day, for **the first 3 weeks** of a 4 week cycle (intake on days 1, 8 and 15 of a 28 day treatment cycle).

Take lenalidomide (25 mg) daily for the first 3 weeks of a 4 week cycle (intake on days 1 to 21 (inclusive) of a 28 day treatment cycle).

Take dexamethasone (40 mg) once a week on the same day each week of a 4 week cycle (intake on days 1, 8, 15 and 22 of a 28 day treatment cycle).

Take lenalidomide and dexamethasone exactly as instructed by your physician; also, be sure to read the relevant patient leaflet and to contact your attending physician and pharmacist for additional information.

Your physician may adjust the dosages of Ninlaro or of the aforementioned medications, or instruct upon their discontinuation due to any side effects that you may experience, or if you suffer from liver or kidney problems.

Do not exceed the recommended dose.

- Swallow Ninlaro capsule whole with water. **Do not** crush, **do not** chew and **do not** open the capsule.
- Avoid direct contact with the capsule contents. If you accidentally get powder from the Ninlaro capsule on your skin, wash the area well with soap and water. If you accidentally get powder from the Ninlaro capsule in your eyes, flush your eyes well with water.
- If you vomit after taking a dose of the medicine, **do not** repeat the dose. Take your next dose of Ninlaro on the next scheduled day and time.

If you have accidentally taken a higher dose, or if a child has accidentally swallowed the medicine, refer immediately to a physician or to a hospital emergency room and bring the medicine package with you.

If you forgot to take the medicine or belatedly remembered that you have to take a dose of Ninlaro, take the missed dose only if there are more than 3 days (72 hours) before the date scheduled for taking the next dose. **Do not** take the missed dose if there are 3 days (72 hours) or less before the date scheduled for taking the next dose.

Adhere to the treatment as recommended by the physician.

Even if there is an improvement in your health, do not stop treatment with this medicine without consulting the physician.

If you stop taking the medicine

Do not change your dose and do not stop taking Ninlaro without consulting the physician.

Do not take medicines in the dark! Check the label and the dose each time you take the medicine. Wear glasses if you need them.

If you have any further questions regarding the use of this medicine, consult the physician or pharmacist.

4. Side effects

As with any medicine, Ninlaro may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not experience any of them.

Ninalro may cause serious side effects, including:

Low platelet count (thrombocytopenia). Low platelet count is a very common side effect associated with the use of Ninlaro (occurred in more than one out of 10 users), and can sometimes be serious. You may need platelet transfusions if your count is too low. Tell your attending physician if you notice any signs of low platelet count, including bleeding and increased tendency to bruise.

Gastrointestinal problems. Diarrhea, constipation, nausea and vomiting are very common side effects associated with the use of Ninlaro (occurred in more than one out of 10 users), and can sometimes be severe. Tell your physician if you experience one or more of these symptoms continuously during treatment with Ninlaro. Your physician may decide to prescribe a medicine to help treat these symptoms.

Neurological problems (Peripheral neuropathy). Neurological problems are very common side effects associated with the use of Ninlaro (occurred in more than one out of 10

users), and may also be severe. Tell your physician if you experience new or worsening of one or more of the following symptoms:

- tingling
- numbness
- pain
- a burning feeling in your feet or hands
- weakness in your arms or legs

Peripheral edema. Edema is a very common side effect associated with the use of Ninlaro (occurred in more than one out of 10 users), and can sometimes be severe. Tell your physician if you develop abnormal swelling of the arms, hands, legs, ankles or feet, or if you have gained weight due to the swelling.

Skin reactions. Tell your physician if you develop a new rash or if an existing rash worsens. This is a very common side effect associated with the use of Ninlaro (occurred in more than one out of 10 users).

Thrombotic microangiopathy (TMA). This is a condition involving blood clots and injury to small blood vessels that may cause harm to your kidneys, brain, and other organs, and may lead to death. Get medical help right away if you get any of the following signs or symptoms during treatment with Ninlaro:

- fever
- bruising
- nose bleeds
- tiredness
- decreased urination

Liver problems. Tell your physician if you experience the following symptoms indicating a liver problem:

- yellowing of the skin or the whites of the eyes
- pain in the right upper stomach area

These are very common side effects associated with the use of Ninlaro (occurred in more than one out of 10 users).

Additional very common side effects (occurred in more than one out of 10 users):

- back pain
- upper respiratory tract infection (cold-like symptoms)
- ocular diseases such as blurred vision, dry eyes and conjunctivitis (eye infection).

Additional common side effects (occurred in less than one out of 10 users):

- skin rash and pain (shingles) as a result of reactivation of the chicken pox virus (herpes zoster).
- lowered white blood cells called neutrophils (neutropenia) that may increase the risk of infection.

Uncommon serious side effects (occurred in less than one out of 1000 users):
Sweet's syndrome (Acute febrile neutrophilic dermatosis) – Acute dermatitis accompanied with fever and neutrophilia.
Stevens-Johnson syndrome – A syndrome manifested by skin blistering and necrosis.
Transverse myelitis – Inflammation of the spinal cord.
Posterior Reversible Encephalopathy Syndrome.
Tumor lysis syndrome – A syndrome resulting from rapid destruction of tumor cells, which is characterized by elevated blood levels of phosphorus and uric acid, reduced levels of calcium and kidney damage.
Thrombotic Thrombocytopenic Purpura – Purpuric rash accompanied with blood clotting and decrease in platelet count.

If you experience any side effect, if any of the side effects worsens, or if you experience a side effect not mentioned in this leaflet, you should consult the physician.

Reporting side effects

Side effects can be reported to the Ministry of Health (MoH) by clicking on the "Report on side effects due to medication therapy" link on the MoH home page (www.health.gov.il) which refers to the online form for side effects reporting, or by entering the link:

https://sideeffects.health.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from the physician.
- Do not use the medicine after the expiry date (exp. date) appearing on the pack. The expiry date refers to the last day of that month.
- Even if stored as recommended, medicines may be kept for a limited period only. Please note the expiry date of this medicine! In case of doubt, consult the pharmacist who dispensed the medicine to you.
- Do not store above 30°C. Do not freeze.
- Store in the original packaging until just before each use.
- Remove the capsule from the blister only at the moment you have to take it.

6. Additional information

In addition to the active ingredient the medicine also contains:
microcrystalline cellulose, talc and magnesium stearate.

Capsule shell and ink contain:
gelatin, titanium dioxide, red iron oxide (Ninlaro 2.3 mg, Ninlaro 4 mg), yellow iron oxide (Ninlaro 4 mg), black iron oxide, shellac, propylene glycol, potassium hydroxide.

What does the medicine look like and what are the contents of the package:

The color of Ninlaro 2.3 mg gelatin capsule is light pink, "Takeda" is printed on its cap and "2.3 mg" is printed on the capsule's body with black ink.
The color of Ninlaro 3 mg gelatin capsule is light grey, "Takeda" is printed on its cap and "3 mg" is printed on the capsule's body with black ink.
The color of Ninlaro 4 mg gelatin capsule is light orange, "Takeda" is printed on its cap and "4 mg" is printed on the capsule's body with black ink.

Each package of the product contains 3 separate blisters. Each blister contains one capsule.

Registration holder: Takeda Israel Ltd., 25 Efal st., Petach-Tikva 4951125

Manufacturer: Takeda Pharma A/S, Dybendal alle 10, DK-2630 Taastrup, Denmark

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
156-81-34609-00/01
156-82-34615-00/01
156-83-34616-00/01

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