PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine is dispensed with a physician's prescription only

Nerlynx

Tablets

The active ingredient and its quantity:

Each tablet contains: 40 mg Neratinib (equivalent to 48.31 mg neratinib maleate)

For inactive and allergenic ingredients in the preparation - see section 6 "Further information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine.
If you have any further questions, consult your 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.

1. WHAT IS THE MEDICINE INTENDED FOR?

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early stage breast cancer with an increased expression of the human epidermal growth factor receptor 2-positive (HER2-positive) who are less than one year from the completion of prior adjuvant trastuzumab based therapy.
Nerlynx in combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 metastatic breast cancer regimens.

Therapeutic group: Antineoplastic drugs, tyrosine kinase inhibitors
Nerlynx acts by blocking HER2 receptors on cancer cells. It aids in stopping cell division and growth.
The HER2 receptor is a protein present on the surface of the cells in the body. It helps control how a healthy breast cell grows. Breast cancer cells displaying multiple HER2 receptors on the surface have faster cell division and growth rates.

2. BEFORE USING THE MEDICINE

X Do not use the medicine if:

You are sensitive (allergic) to the active ingredient (neratinib) or to any of the additional ingredients that the medicine contains (see section 6 "Further information").

! Special warnings regarding use of the medicine

Before treatment with Nerlynx, tell the physician if:

- You have liver problems. You may need to take a lower dose of Nerlynx.
- You are pregnant or plan to become pregnant. Nerlynx can harm your unborn baby.
- You are breastfeeding or plan to breastfeed. Do not breastfeed during the treatment and for at least one month after taking your last dose of the medicine.

You should take an antidiarrheal medicine when starting treatment with Nerlynx.
Nerlynx tends to cause diarrhea at an early stage of treatment. You should take an antidiarrheal medicine to moderate the diarrhea and to avoid dehydration of the body from loss of body salts and fluids during treatment with Nerlynx. (See section 3 - How Should You Use the Medicine?)

! Children and adolescents

This medicine is not intended for children and adolescents under 18 years old.
No information is available regarding the safety and efficacy of using this medicine in children and adolescents under 18 years old.

! Tests and follow-up

Nerlynx can cause changes in liver function, which can be detected in blood tests. Both before and after starting treatment with the medicine, the physician will refer you for monthly blood tests during the first three months, and then every three months as needed during treatment with Nerlynx. The physician will stop treatment with Nerlynx if results of liver function tests show severe problems.

! Drug interactions

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

Certain medicines may affect the activity of Nerlynx or may increase the likelihood of having side effects. Likewise, Nerlynx may affect the activity of certain other medicines, therefore, the use of them together with Nerlynx is not recommended.

Tell your physician if you are taking any of the following medicines:

• Antifungal medicines such as ketoconazole or fluconazole
• Antibiotics for treatment of bacterial infection, such as erythromycin or clarithromycin
• Medicine for tuberculosis - rifampicin
• Protease inhibitors - antiviral medicines
• Anticonvulsant medicines - carbamazepine, phenobarbital or phenytoin
• An herbal product for treating depression - St. John's wort
• Medicines for hypertension and chest pain - diltiazem or verapamil
• Medicine for heart conditions - dabigatran or digoxin
• Medicine for treating allergic rhinitis - fexofenadine
• If you are taking medicines for stomach problems such as:
  - Lansoprazole, omeprazole or similar medicines called "proton pump inhibitors" - these medicines should be avoided during treatment with Nerlynx.
  - Ranitidine, cimetidine or similar medicines called "H_2 receptor blockers". Nerlynx should be taken two hours before or ten hours after these medicines are taken.
  - Tums (calcium carbonate) - antacid medicines - Nerlynx should be taken at least 3 hours after taking antacid medicines.

! Use of the medicine and food

Take the medicine with food.

Do not take grapefruit while you are taking Nerlynx – this includes any food, juice or nutritional supplements which may contain grapefruit. The reason for this is that grapefruit may interact with Nerlynx and affect the mechanism of action of the medicine.

! Pregnancy, breastfeeding and fertility

Consult your physician before using the medicine if you are pregnant, planning to become pregnant or breastfeeding.

Pregnancy

Based on the mechanism of action of the medicine and findings from animal studies, Nerlynx may cause harm to the fetus when given to a pregnant woman. There is no information available regarding pregnant women and the risk related to the medicine.

Females who can become pregnant should:

- Undergo testing for pregnancy before starting to take the medicine.
- Use an effective contraceptive method during treatment and for at least one month after taking the last dose of Nerlynx.
- Discuss with the physician as to which contraceptive methods may be used during treatment.
- Tell your physician immediately if you have become pregnant during treatment with Nerlynx.

Males with female partners who can become pregnant should use an effective contraceptive method (e.g., condoms) during the treatment and for three months after the last dose of Nerlynx has been taken.

Breastfeeding

It is not known whether Nerlynx or its metabolites pass into breast milk. It is also unclear whether it effects breast milk production or it effects the breastfeeding baby. There is a risk of severe side effects to the breastfeeding baby. Consequently, breastfeeding is not recommended while taking the medicine, nor for at least one month after taking the last dose of the medicine.

! Driving and using machines

Nerlynx has a mild or moderate effect on the ability to drive and use machines. The side effects of Nerlynx (e.g., dehydration and dizziness caused from diarrhea, fatigue and fainting) may affect tasks which require judgement and motor or cognitive skills.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation in accordance with the physician's instructions.

You should check with the physician or pharmacist if you are not sure about the dosage or

treatment regimen of the preparation.
The dosage and treatment regimen will be determined by the physician only.
The usual dose is:

For extended adjuvant treatment of early stage breast cancer:

6 tablets of Nerlynx once daily (total of 240 mg). The treatment duration is until disease recurrence or up to one year.

For treatment of advanced or metastatic breast cancer:

6 tablets of Nerlynx once daily (total of 240 mg) on Days 1-21 of a 21-day cycle combined with capecitabine (750 mg/m^2 given orally twice daily) on Days 1-14 of a 21-day cycle until disease progression or unacceptable toxicity.

Swallow the medicine with water at approximately the same time each day.

Take antidiarrheal medicines when starting treatment with Nerlynx.
A common side effect of Nerlynx which may be severe is diarrhea. You may become dehydrated from loss of body salts and fluids. When you start Nerlynx, your physician should prescribe the medicine loperamide for you during the first two months (56 days) of treatment, and then as needed. Start taking antidiarrheal medicines with the first dose of Nerlynx.

To help prevent or reduce diarrhea:

- You should start taking loperamide with the first dose of Nerlynx.
- Continue taking loperamide during the first two months (56 days) of treatment with Nerlynx, and then as needed. Your physician will tell you how often to take this medicine.
- Your physician may also need to give you other medicines to manage diarrhea when you start treatment with Nerlynx. Follow the instructions on how to use these medicines.
- Take antidiarrheal medicines exactly according to the physician's instructions.
- While taking antidiarrheal medicines, try to keep the number of bowel movements each day (one or two).
- Tell your physician if you have more than two bowel movements in one day, or you have diarrhea that does not go away.
- After two months (56 days) of treatment with Nerlynx, follow your physician's instructions regarding taking loperamide as needed to control diarrhea.
- Your physician may change the dose, temporarily stop or completely stop Nerlynx to manage your diarrhea.

Method of administration:
Do not exceed the recommended dose.
Swallow the tablets with food. Do not chew, crush or split the tablets.

If you have accidentally taken a higher dose, consult a physician or proceed to a hospital emergency room immediately and bring the package of the medicine with you. You may experience diarrhea, nausea, vomiting and dehydration.

If you forget to take this medicine at the scheduled time, wait until the next day to take the next dose. Do not take a double dose.

Treatment should be continued as recommended by the physician.
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting with your physician.

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

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

4. SIDE EFFECTS

Like all medicines, the use of Nerlynx may cause side effects in some users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.

Diarrhea
Nerlynx may cause diarrhea early during treatment unless antidiarrheal medicines are taken to prevent or reduce diarrhea. The diarrhea may be severe, causing dehydration.

Consult a physician immediately if:

You have severe diarrhea or if you have diarrhea along with weakness, dizziness or fever.

The following side effects may be severe:

• Diarrhea
• Vomiting
• Dehydration
• Cellulitis
• Kidney failure
• Erysipelas (a type of skin infection)
• Elevated ALT liver enzymes
• Elevated AST liver enzymes
• Nausea
• Fatigue
• Stomach-area (abdomen) pain

Liver problems

Nerlynx can cause changes in liver function - these can be diagnosed by blood tests. You may or may not have signs or symptoms of liver problems. The physician will perform blood tests before and during treatment with Nerlynx. If your liver tests indicate severe problems your physician will stop treatment with Nerlynx. Contact your physician immediately if the following side effects appear or if you develop any other symptoms of liver problems:
• Tiredness
• Nausea
• Vomiting
• Pain in the upper stomach-area (abdomen)
• Fever
• Rash
• Itching
• Yellowing of your skin or whites of your eyes

Additional side effects:

Very common side effects (may occur in more than 1 in 10 users):
• Diarrhea
• Nausea
• Stomach-area (abdomen) pain (in either upper or lower abdomen)
• Tiredness
• Vomiting
• Rash
• Dry or inflamed mouth, or mouth sores
• Decreased appetite
• Muscle spasms
• Upset stomach

Common side effects (may occur in 1-10 users out of 100):
• Elevated ALT liver enzymes
• Nail problems including color change
• Elevated AST liver enzymes
• Dry skin
• Urinary tract infection
• Weight loss
• Swelling of your stomach-area
• Nosebleed
• Dehydration
• Dry mouth
• Skin fissures

Side effects of Nerlynx in combination with capecitabine:

Very common side effects (may occur in more than 1 in 10 users):
• Diarrhea
• Nausea
• Vomiting
• Tiredness, weakness
• Decreased appetite
• Constipation
• Weight loss
• Dizziness

Common side effects (may occur in 1-10 users out of 100):
- Joint pain
- Back pain
- Urinary tract infection
- Upper respiratory tract infection
- Swelling of your stomach-area
- Kidney failure (including acute kidney injury, blood creatinine increased, renal failure, and renal impairment)
- Muscle spasms
- Pain when urinating
- Malaise
- Influenza like illness

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your physician.

Reporting side effects:

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects of Drug Treatment" on the Ministry of Health homepage (www.health.gov.il) which links to an online form for reporting side effects, or by the following link: https://sideeffects.health.gov.il.

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without explicit instruction from your physician.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

Storage conditions:

Store below 25°C.

Once opened, use within 31 days and store in tightly closed packaging to protect from moisture.

6. FURTHER INFORMATION

In addition to the active ingredient the medicine also contains:

Tablet core:

- Mannitol, microcrystalline cellulose, crospovidone (type A), povidone (k-25), colloidal silicon dioxide, magnesium stearate (vegetable grade) and purified water.

Tablet film coating:

- Polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide red.

What the medicine looks like and the contents of the pack:

The tablet is film-coated, red, oval shaped and debossed with 'W104' on one side and plain on the other side.

Nerlynx film-coated tablets are packed in a white, round bottle, with a child-resistant closure.

Each bottle contains 180 film-coated tablets.

Each bottle contains a desiccant (silica gel). Do not swallow the desiccant.

Registration holder's name and address:

Medison Pharma Ltd., 10 Hashiloach St., Petach Tikva.

Manufacturer's name and address:

Puma Biotechnology, Inc., 10880 Wilshire Blvd., Suite 2150
Los Angeles, CA 90024, USA

This leaflet was revised in December 2021 according to Ministry of Health guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 164-61-35663