Patient Leaflet According to the Pharmacists' Regulations (Preparations) – 1986
This medicine is sold with a doctor's prescription only.

Akynzeo
Capsules

Active ingredients:
Each capsule contains 300 mg of netupitant and 0.5 mg of palonosetron as hydrochloride salt.
For a list of inactive ingredients, please see section 6. See also 'Important information about some of the medicine's ingredients' in section 2.

Read this entire leaflet carefully before using this medicine.
This leaflet contains concise information about the medicine. If you have any further questions, please refer to your doctor or pharmacist.
This medicine was prescribed for treating your condition. Do not pass it on to others. It may harm them even you think their medical condition is similar to yours.
The medicine is intended for adults over 18 years of age.

1. What is the medicine intended for?
This medicine is intended for prevention of nausea and vomiting as an immediate or delayed result of chemotherapy treatment.
Therapeutic Group:
Anti-nausea and vomiting agents: Netupitant – blocks substance P from binding to neurokinin 1 (NK-1) receptor, Palonosetron – blocking serotonin (5-HT_3) receptor.

By blocking the activity of substance P and serotonin, the medicine prevents stimulation of the vomiting center and as a result, also the feeling of nausea.

2. Before using the medicine
Do not use the medicine if:

- You are sensitive (allergic) to the active ingredients or to any of the other ingredients this medicine contains (for the list of inactive ingredients, please see section 6).
- You are pregnant.

Special warnings regarding the use of this medicine:

Before the treatment with the medicine tell your doctor if:

- You suffer from liver or kidney problems.
- You suffer from bowel obstruction or have suffered in the past from constipation.
- You or someone in your family suffer or have suffered in the past from a heart problem called QT interval prolongation, or if you suffer from any other heart problem.
- You suffer from imbalance of salts (electrolytes) in your blood (e.g. potassium or magnesium).

If you are taking or have recently taken any other medicines, including non-prescription medicines and nutrition supplements, please tell your doctor or pharmacist. Especially inform your doctor or pharmacist if you are taking the following medicines (it should be noted that the following list mentions the active ingredients of the medicines. If you are unsure whether you are using one of these medicines, please consult with your doctor or pharmacist):

- Certain medicines for the treatment of depression and anxiety from the SSRIs or SNRIs groups such as: fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, venlafaxine, duloxetine.

Also, inform your doctor if you are being treated with one of the following medicines, because the doctor may change their dosage, for instance:

- Medicines that affect the heart rate (medicines for treatment of heart rhythm disturbances or other medicines that might cause irregular heartbeats), such as amiodarone, nicardipine, quinidine, moxifloxacin, haloperidol, chlorpromazine, quetiapine, thioridazine, domperidone.
- Certain chemotherapy medicines such as docetaxel, etoposide, irinotecan.
- Rifampicin, erythromycin (antibiotic), dexamethasone, ketoconazole.
- The anxiolytic midazolam.
- Cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, fentanyl, diergotamine, ergotamine.
- Zidovudine, valproic acid, morphine, digoxin, dabigatran, colchicine.

Use of this medicine and food: this medicine can be taken independently of mealtimes.

Pregnancy and breastfeeding:

- Before starting the treatment, a pregnancy test should be performed to ensure you are not pregnant.
- Use contraceptives, as recommended by your doctor, during the treatment and for a month after the treatment ends.
- Do not use the medicine if you are pregnant or if you might become pregnant and are not using contraceptives.
- Do not breastfeed while using the medicine and until a month after you stop using it.
- Consult your doctor if you are planning a pregnancy or think you are pregnant.

Driving and use of machinery: the use of this medicine may cause dizziness and/or tiredness. If you experience these effects, do not drive or operate machinery.

Use in children: do not use in children and adolescents under 18 years of age.

Important information about some of the medicine's ingredients:

- The capsules contain sucrose and sorbitol (types of sugar). See section 6 for the quantities of sugar and details of additional inactive ingredients.
- The capsules might contain traces of lecithin derived from soya. If you are allergic to peanuts or soya and you observe any sign of an allergic reaction, contact your doctor immediately. Symptoms of allergic reaction may include: urticaria (raised and itchy skin rash), skin rash, itching, breathing or swallowing difficulties, swelling of the mouth, face, lips, tongue or throat; sharp drop in blood pressure.

3. How to use this medicine?

Always use according to the doctor's instructions. Check with your doctor or pharmacist if you are not sure.
The dosage and the manner of treatment will be determined by the doctor only.
The standard dosage is usually: one capsule, about an hour before the chemotherapy treatment. Swallow the capsule whole.
Do not exceed the recommended dose.
This medicine can be taken independently of mealtimes.

If you have accidentally taken a higher dosage or if a child has accidentally swallowed the medicine, go immediately to a doctor or a hospital emergency room and bring the medicine package with you.
If you forgot to take the medicine tell your doctor.
If you stop taking the medicine: the medicine is taken to help prevent nausea and vomiting as a result of chemotherapy treatment. If you do not wish to use it, consult with your doctor. If you

decide not to use this medicine (or a similar medicine), the chemotherapy treatment is liable to cause you nausea and vomiting.

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 the doctor or pharmacist.

4. Side Effects

Like any medicine, the use of Akynzeo may cause side effects in some users. If the side effects are bothersome, get worse or persist, consult your doctor. Do not be alarmed while reading the list of side effects, you may not suffer from any of them.

Stop the treatment and proceed immediately to your doctor or to a hospital emergency room if the following serious side effects appear:

- Severe allergic reaction. Symptoms of severe allergic reaction include: urticaria, skin rash, itching, breathing or swallowing difficulties, swelling of mouth, face, lips, tongue or throat; sharp drop in blood pressure (very rare side effects, *appear in less than 1 user out of 10,000).*

Additional Side Effects:

Common side effects (appear in 1-10 users out of 100): headache, constipation, tiredness.

Uncommon side effects (appear in 1-10 users out of 1,000):

- Hair loss, weakness, decreased appetite, high blood pressure, urticaria (raised and itchy skin rash), heart muscle problems, ECG problems, vertigo (spinning sensation), dizziness, insomnia, abdominal problems including: discomfort, nausea, pains, indigestion, hiccups, flatulence or diarrhea.
- Changes seen in blood tests: high levels of certain enzymes (including blood and liver enzymes); high creatinine levels (kidney function tests); low neutrophils levels (type of white blood cells that fight infections); high levels of white blood cells.

Rare side effects (appear in 1-10 users out of 10,000):

- Back pain, feeling hot, sleep problems, low blood pressure, chest pain (not related to the heart), numbness, sudden nervous breakdown, mood changes, bladder infection and inflammation, conjunctivitis (type of eye infection), blurred vision, low potassium levels (seen in blood tests), change or disturbance in heart rhythm, heart valve problems, decrease in blood flow to the heart muscle, tongue coating, swallowing difficulties, aftertaste after taking the medicine.
- Other changes seen in blood tests: high levels of creatine phosphokinase MB (indicating a sudden decrease in blood flow to the heart), high troponin levels (indicating heart dysfunction), high bilirubin levels (indicating liver dysfunction), high levels of certain white blood cells called lymphocytes, low white blood cell levels.

If you experience any side effects that are not mentioned in this leaflet or if there is any change in your general feeling, consult the doctor immediately!

Side effects may be reported to the Ministry of Health by clicking on the link "Report on side effects following medicinal treatment" on the homepage of the Ministry of Health website (www.health.gov.il) which leads you to the online form for reporting side effects, or by entering the link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine, and any other medicine, must be stored in a safe place out of the reach of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.

- Storage conditions: store below 30^0C.

6. Additional information

In addition to the active ingredients, the capsules also contain the following inactive ingredients:

Microcrystalline cellulose, sucrose lauric acid esters, povidone K-30, croscarmellose sodium, purified water, silicon dioxide/ silica colloidal hydrated, sodium stearyl fumarate, magnesium stearate(vegetable grade), glycerol monocaprylocaprate (type I), glycerin (anhydrous), polyglyceryl oleate, butylated hydroxyanisole, gelatin (type 195), sorbitol (A810, 50/50 w/glycerin), titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), shellac glaze (partially esterified), iron oxide black (E172), propylene glycol.

- The capsules contain sucrose, sorbitol and might also contain traces of soya. See also section 2, 'Important information about some of the medicine's ingredients'.
- Each capsule contains 7 mg sorbitol and 20 mg sucrose.

What does the medicine look like and what does the package contain?

The package contains one white-caramel colored capsule with 'HE1' printed on it.

Registration holder: Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.
Manufacturer: Helsinn Birex Pharmaceuticals Ltd., Dublin, Ireland.
Medicine registration number in the National Medicines Registry of the Ministry of Health: 1557934343

This leaflet was checked and approved by the Ministry of Health in March 2016.

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