Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Zykadia™ 150 mg
Hard gelatin capsules

Active ingredient:
Each capsule contains ceritinib 150 mg
Inactive ingredients– see section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

The medicine is intended for use in adults, 18 years of age and older.

1. What is this medicine intended for?
Zykadia is indicated for the treatment of people with non-small cell lung cancer (NSCLC) that is caused by a defect in a gene called anaplastic lymphoma kinase (ALK) and has spread to other parts of the body.

Therapeutic group:
Zykadia belongs to a class of drugs called antineoplastics that stop the development of new cancer cells when the cancer is caused by a defect in a gene called anaplastic lymphoma kinase (ALK). Zykadia slows down the growth and spread of NSCLC that is ALK positive.

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

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients in this medicine. For a list of the inactive ingredients, see section 6 'Additional information'.

Special warnings about using this medicine
Before you take Zykadia, tell your doctor about your medical condition, including if:
- you have liver problems
- you have problems with your lungs or problems breathing
- you have diabetes or high blood sugar
- you have heart problems, including a condition called long QT syndrome
- you have or have had inflammation of the pancreas (pancreatitis)
- you are pregnant, planning to become pregnant or are breastfeeding (see also below under 'Pregnancy and breastfeeding').
- you are a man with a female partner who is able to become pregnant (see also below under 'Pregnancy and breastfeeding').

Zykadia may cause gastrointestinal problems, liver toxicity, lung disease, prolonged QT interval, high blood sugar levels, slow heart rate (bradycardia), inflammation of the pancreas (pancreatitis) - see list in section 4 'Side effects'.

Risk of sensitivity to sunlight (photosensitivity). Avoid spending time in sunlight during treatment with Zykadia. Your skin may be sensitive to the sun, and you may burn more easily. Use sunscreen and wear clothing that covers your skin to protect against sunburn.

Children and adolescents
Zykadia is not intended for use in children and adolescents under the age of 18.

Tests and follow-up
Your doctor should do blood tests at least every month to check your liver as long as you are taking Zykadia.
Your doctor will check your blood sugar level before you start treatment with Zykadia and as needed during treatment.
Your doctor should do blood tests to check your lipase and amylase levels before you start treatment with Zykadia and as needed during treatment.
Your doctor may check your heart, blood pressure and lungs during treatment with Zykadia.

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:

Effect of other medicines on Zykadia
Strong CYP3A inhibitors
Strong CYP3A4/P-gp inhibitors (e.g. ritonavir, ketoconazole, telithromycin) increase the concentration of ceritinib, which may increase the incidence and severity of the side effects of Zykadia. Avoid concurrent use of strong CYP3A inhibitors during treatment with Zykadia. If combined treatment is unavoidable, your doctor will reduce the dose of Zykadia.

Strong CYP3A inducers
Strong CYP3A4/P-gp inducers (e.g. rifampin, carbamazepine, phenytoin, St. John's Wort) reduce the concentration of ceritinib, which may reduce the effectiveness of Zykadia. Avoid concurrent use of strong CYP3A inducers during treatment with Zykadia.

Effect of Zykadia on other medicines
CYP3A substrates
Ceritinib increases the concentration of sensitive CYP3A substrates (e.g. midazolam). Avoid coadministration of Zykadia with sensitive CYP3A substrates. If coadministration is unavoidable, your doctor will consider reducing the dose of the sensitive CYP3A substrate.

CYP2C9 substrates
Ceritinib increases the concentration of CYP2C9 substrates (e.g. warfarin). Increase the frequency of INR monitoring if coadministration of warfarin with Zykadia is unavoidable as the anti-coagulant effect of warfarin may be enhanced.
Avoid coadministration of Zykadia with CYP2C9 substrates for which small concentration changes may lead to severe toxicity. If coadministration is unavoidable, your doctor will consider reducing the dosage of the sensitive CYP2C9 substrate.

Medicines that prolong QT interval
Zykadia causes concentration-dependent prolongation in the QT interval. Avoid coadministration of Zykadia with other medicines known to prolong the QT interval.

Medicines that cause bradycardia
Zykadia may cause bradycardia (slow heart rate). Avoid coadministration of Zykadia with other medicines known to cause bradycardia.

Using this medicine and food
Take Zykadia with food.
You should not drink grapefruit juice or eat grapefruit during treatment with Zykadia. It may increase the amount of Zykadia in your blood to a harmful level.

Pregnancy and breastfeeding
Pregnancy
Zykadia can harm your unborn baby. Women who are able to become pregnant should use an effective method of birth control during treatment with Zykadia and for 6 months after stopping treatment with Zykadia. Talk to your doctor about birth control that may be right for you. **Tell your doctor right away** if you become pregnant or think that you may be pregnant.

- Men with female partners who are able to become pregnant should use condoms during treatment with Zykadia and for 3 months after stopping treatment with Zykadia.

Breastfeeding
It is not known if Zykadia passes into your breast milk. Do not breastfeed during treatment with Zykadia and for two weeks after stopping treatment with Zykadia.

3. How to use this medicine?
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually 450 mg daily.
Your doctor may change the dosage or stop use of the medicine due to side effects.
Patients with severe liver impairment will receive a lower dose of Zykadia.
You should take Zykadia once daily.
Take Zykadia with food.
If you vomit after taking Zykadia, do not take an additional dose. Continue with the next scheduled dose.
Swallow the capsules whole with water. Do not chew or crush the capsules.

Do not exceed the recommended dose.
Continue taking Zykadia for as long as your doctor tells you.
Treatment with Zykadia is long term, possibly lasting for months. Your doctor will check your condition to see that the treatment is having the desired effect.

If you have accidentally taken a higher dose
If you have taken an overdose or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine
If you forgot to take this medicine at the required time, take it as soon as you remember. If your next dose is within the next 12 hours, skip the missed dose. Take the next dose at the usual time. Do not take a double dose.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor or pharmacist.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects
Like with all medicines, using Zykadia may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

Zykadia may cause serious side effects, including:
Stomach and intestinal (gastrointestinal) problems. Zykadia may cause stomach and intestinal problems (very common), including diarrhea, nausea, vomiting, and stomach-area pain. Follow your doctor's instructions about taking medicines to help with these symptoms. Contact your doctor if your symptoms are severe or cannot be tolerated.

Liver problems. Zykadia may cause liver injury. Your doctor should do blood tests at least every month to check your liver during treatment with Zykadia. **Tell your doctor right away** if:

- you feel tired (very common)
- your skin or the whites of your eyes turn yellow
- you have a decreased appetite (very common)
- your urine turns dark or brown (tea color)
- you have itchy skin
- you have nausea or vomiting
- you have pain on the right side of your stomach-area
- you bleed or bruise more easily than normal

Lung problems (pneumonitis). Zykadia may cause severe or life-threatening inflammation of the lungs during treatment that can lead to death. The symptoms may be similar to the symptoms of lung cancer. **Tell your doctor right away** if you have any new or worsening symptoms, including:

- trouble breathing or shortness of breath
- fever
- cough with or without mucus
- chest pain

Heart problems. Zykadia may cause very slow, very fast, or abnormal heartbeats. Your doctor may check your heart during treatment with Zykadia. **Tell your doctor right away** if you feel new chest pain or discomfort, dizziness or lightheadedness, if you faint or have abnormal heartbeats, palpitations. Inform your doctor if you start to take or have any change in heart or blood pressure medicines.

High blood sugar levels (hyperglycemia). People with diabetes or glucose intolerance or who take corticosteroids have an increased risk of high blood sugar during treatment with Zykadia. Your doctor will check your blood sugar level before starting treatment with Zykadia and as needed during treatment with Zykadia. **Call your doctor right away** if you have any symptoms of high blood sugar, including:

- increased thirst
- increased hunger
- headaches
- trouble thinking or concentrating
- urinating often
- blurred vision
- tiredness
- your breath smells like fruit

Inflammation of the pancreas (pancreatitis). Zykadia can cause pancreatitis that has led to death. You may develop increased pancreatic enzyme blood levels, which may be a sign of pancreatitis. The signs and symptoms of pancreatitis include upper abdominal pain that may spread to the back and get worse with eating. Your doctor should do blood tests to check your pancreatic enzyme blood levels before you start treatment with Zykadia and as needed during your treatment.

Additional side effects
Very common side effects (may affect more than 1 in 10 users):
Constipation, heartburn (sign of a potential problem of the esophagus), tiredness, non-cardiac chest pain, back pain, pain in extremities, pain in muscles and/or bones, itching, fever, decreased appetite, weight loss, cough, headache, dizziness, prolonged QT interval, rash, anemia (reduction in the number of red blood cells), neutropenia (reduction in the number of white blood cells), thrombocytopenia (reduction in the number of platelets in the blood), abnormal liver function results in blood tests (increase in levels of enzymes called alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or gamma glutamyl transferase (GGT) and/or alkaline phosphatase, high levels of bilirubin), abnormal kidney function results in blood tests (high level of creatinine), low level of phosphate in the blood, high levels of amylase and lipase in the blood (pancreatic enzymes).

Common side effects (may affect 1-10 in 100 users):
Vision disturbances, neuropathy, kidney failure, dehydration, seizures, inflammation of the pericardium (pericarditis).

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 doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Do not store above 30°C.

6. Additional information

- **In addition to the active ingredient, this medicine also contains:**
  Microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide.
  Ingredients of the gelatin capsule:
  Gelatin, titanium dioxide (E171), indigotine – FD&C Blue 2 (E132), printing ink, black
  Ingredients of the ink imprinted on the capsule:
  Shellac glaze 45%, iron oxide black (E172), propylene glycol, ammonium hydroxide 28%
  Each dose contains 1.54 mg sodium.

- **What the medicine looks like and contents of the pack:**
  The body of the capsule is opaque white, and the cap of the capsule is opaque blue. "NVR" is imprinted on the body of the capsule (the white part), and "LDK 150MG" is imprinted on the cap of the capsule (the blue part). The imprint is in black.
  Pack size: 90 or 150 capsules in a blister pack. Not all pack sizes may be marketed.

- **Registration holder's name and address:** Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

- Revised in February 2022 according to MOH guidelines.

- Registration number of the medicine in the Ministry of Health's National Drug Registry: 153 87 34228