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

Kalydeco 50 mg granules
Kalydeco 75 mg granules
Kalydeco 150 mg film coated tablets

Active ingredients and their quantities
Kalydeco 50 mg granules
Each sachet of granules contains ivacaftor 50 mg

Kalydeco 75 mg granules
Each sachet of granules contains ivacaftor 75 mg

Kalydeco 150 mg film coated tablets
Each tablet contains ivacaftor 150 mg

Inactive ingredients and allergens - see section 6 **"Additional information"**. See also **"Important information about some of this medicine's ingredients"** in section 2.

Read this entire leaflet carefully before you/your child start using this medicine. This leaflet contains concise information about this medicine. If you have further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat you/your child's illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is the medicine intended for?
Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R.*

Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*.

Kalydeco is not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.

Kalydeco contains the active ingredient ivacaftor. Ivacaftor acts at the level of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that forms a channel at the cell surface that allows the movement of particles such as chloride ions in and out of the cell. Due to mutations in the *CFTR* gene (see below), chloride movement is reduced in those with cystic fibrosis (CF). Ivacaftor helps certain abnormal CFTR proteins open more often to improve chloride movement in and out of the cell.

Therapeutic group: Potentiator of the CFTR protein

2. Before using the medicine

Do not use this medicine if:
- You/your child are sensitive (allergic) to the active ingredient (ivacaftor) or to any of the other ingredients in this medicine (see section 6 **"Additional information"**).

Special warnings about using this medicine

Before taking Kalydeco, tell your doctor if:
- you/your child have liver problems or have previously had them. The doctor may need to adjust the dosage for you/your child.
- you/your child have kidney problems or have previously had them.
- you/your child have had an organ transplant. Kalydeco is not recommended for patients who have undergone an organ transplant.
- Kalydeco should only be used if you/your child have one of the mutations in their *CFTR* gene indicated in section 1 (**What is the medicine intended for?**).

Increased liver enzymes in the blood have been seen in some patients receiving Kalydeco. Contact the doctor right away if you/your child have any of these symptoms, which may be a sign of liver problems:
- Pain or discomfort in the upper right stomach area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Children
Kalydeco granules are not intended for use in children under two years of age.
Kalydeco tablets are not intended for use in children under 6 years of age.

Tests and follow-up
The doctor will do some blood tests to check your/your child's liver function before and during treatment, particularly during the first year and especially if you/your child have had high liver enzymes in the past.

Abnormality of the eye lens (cataract) without any effect on vision has been noted in some children and adolescents treated with Kalydeco. The doctor may perform some eye examinations prior to and during treatment.

Drug interactions
If you/your child are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.

Kalydeco may affect the way other medicines work, and other medicines may affect how Kalydeco works or make side effects more likely. In particular, tell your doctor if you/your child are taking or might take any of the medicines listed below. The doctor may decide to adjust your/your child's dose or that you need extra check-ups.

- **Antifungal medicines** (used for the treatment of fungal infections) such as fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole

- **Antibiotic medicines** (used for the treatment of bacterial infections) such as clarithromycin, erythromycin, rifabutin, rifampicin, and telithromycin
- **Epilepsy medicines** (used for the treatment of epileptic seizures) such as carbamazepine, phenobarbital, and phenytoin
- **Herbal medicines** such as Hypericum perforatum (St. John's wort)
- **Immunosuppressants** (used after an organ transplantation) such as cyclosporin, everolimus, sirolimus, and tacrolimus
- **Cardiac glycosides** (used for the treatment of some heart conditions) such as digoxin
- **Anticoagulant medicines** (used to prevent blood clots) such as warfarin
- **Medicines for diabetes** such as glimepiride and glipizide
- **Medicines for lowering blood pressure** such as verapamil

Using this medicine and food
Avoid food or drink containing grapefruit during treatment with Kalydeco as they may increase the side effects of Kalydeco by increasing the amount of ivacaftor in your/your child's body. Take Kalydeco tablets with food that contains fat. Examples of meals or snacks that contain fat include those prepared with butter or oils or those containing eggs. Other fat-containing foods are:

- Cheese, whole milk, whole-milk dairy products, yogurt, chocolate
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, consult a doctor before using this medicine. It may be better to avoid using Kalydeco during pregnancy, if possible. The doctor will help you to decide what is best for you and your child.

It is unknown whether ivacaftor is secreted in a mother's milk. If you are planning to breastfeed, consult your doctor before taking Kalydeco. Your doctor will decide whether to recommend that you stop breast-feeding or for you to stop ivacaftor therapy. Your doctor will take into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines
Kalydeco can cause dizziness. If you/your child feel dizzy, do not drive, cycle or use machines.

Important information about some of this medicine's ingredients
Kalydeco contains lactose. If you/your child have been told by the doctor that you/your child have intolerance to some sugars, contact the doctor before taking this medicine.

Kalydeco contains less than 23 mg sodium per dose, that is to say essentially 'sodium free'.

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.

Kalydeco dosing recommendations are provided in Table 1.

Table 1: Dosing recommendations for patients aged 2 years and older

Age/Weight	Dose	Total daily dose
2 to 5 years old, less than 14 kg	One sachet of 50 mg granules taken orally every 12 hours with fat containing food	100 mg
2 to 5 years old, 14 kg to less than 25 kg	One sachet of 75 mg granules taken orally every 12 hours with fat-containing food	150 mg
6 years and older, 25 kg or more	150 mg tablet taken orally every 12 hours with fat-containing food	300 mg

Take the morning and evening doses approximately 12 hours apart with food that contains fat.

If you/your child have liver problems, either moderate or severe, your doctor may need to reduce the dose because your liver will not clear the medicine as fast as in people who have normal liver function.

- Moderate liver problems: the dose may be reduced to one 150 mg tablet once daily (for patients weighing 25 kg or more), one sachet once daily (50 mg for children weighing less than 14 kg or 75 mg for children weighing 14 kg to less than 25 kg).
- Severe liver problems: the use is not recommended but your/your child's doctor may decide if it is appropriate for you/your child to use this medicine in which case the dose must be reduced to one 150 mg tablet every other day or less frequently (for patients weighing 25 kg or more), or one sachet every other day (50 mg for children weighing less than 14 kg or 75 mg for children weighing 14 kg to less than 25 kg).

Kalydeco is for oral use.

<u>Film-coated tablets</u>
Swallow the tablet whole. There is no information about breaking, chewing or dissolving the tablets. The recommended dosage for children weighing less than 25 kg cannot be obtained with Kalydeco tablets.

<u>Granules in sachet</u>
Each sachet is for single use only.

Giving Kalydeco to your child
- Hold sachet of granules with dotted line on top.
- Shake sachet gently to settle contents.
- Tear or cut sachet open along dotted line.
- Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid. Food or liquid should be at room temperature or below. Some examples of age-appropriate soft foods or liquids include puréed fruits or vegetables, yogurt, applesauce, water, milk, breast milk, infant formula, or juice.
- Once mixed, give the product to your child immediately. If this is not possible, give it within the following hour after mixing. Ensure that the mixture is completely and immediately consumed.

- A fat-containing meal or snack should be given to your child just before or just after dosing (see "**Using this medicine and food"** in section 2).

Do not exceed the recommended dose.

If you/your child have accidentally taken a higher dosage
You/your child may experience side effects, including those mentioned in section 4 below. If you/your child have taken an overdose, or if a child has accidently swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you/your child forgot to take this medicine at the scheduled time, take the missed dose if less than 6 hours have passed since the time when you/your child was supposed to take the medicine. Otherwise, wait until the next scheduled dose as you/your child normally would. Do not take a double dose to make up for a forgotten 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.

If you/your child stop taking the medicine, tell your doctor. Before stopping you should discuss the implications with your doctor or the pharmacist.

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 about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using Kalydeco may cause side effects in some users. Do not be alarmed by this list of side effects; You/your child may not experience any of them.

Serious side effects
Stomach ache and increased liver enzymes in the blood.

Possible signs of liver problems
Increased liver enzymes in the blood are common in patients with CF. **Tell your doctor straight away if** you/your child get any of the following signs which may indicate liver problems:
- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Very common side effects (occur in more than one in ten users)
- Upper respiratory tract infection (common cold), including sore throat and nasal congestion
- Headache
- Dizziness
- Diarrhoea

- Stomach pain
- Changes in the type of bacteria in mucus
- Increased liver enzymes (signs of stress on the liver)
- Rash

Common side effects (occur in 1-10 in 100 users)
- Runny nose
- Ear pain, ear discomfort
- Ringing in the ears
- Redness inside the ear
- Inner ear disorder (feeling dizzy or spinning)
- Sinus congestion
- Redness in the throat
- Breast mass

Uncommon side effects (occur in 1-10 in 1,000 users)
- Ear congestion
- Breast inflammation
- Enlargement of the breast in males
- Nipple changes or pain

Side effects in children
Side effects seen in children are similar to those observed in adults and adolescents. However, increased liver enzymes in the blood are more frequently seen in young children.

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

Reporting side effects
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 the doctor.

Do not use Kalydeco 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
Store below 30°C.

Kalydeco granules should be used within an hour of mixing the granules with food.

6. Additional information
In addition to the active ingredient, the medicine also contains:

Kalydeco film-coated tablets

- Tablet core contains microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate , colloidal silicon dioxide.
- Tablet coating contains polyvinyl alcohol, titanium dioxide, PEG 3350, talc, FD&C Blue #2/indigo carmine aluminum lake, carnauba wax.
- Printing ink contains shellac, isopropyl alcohol, iron oxide black, n-butyl alcohol, propylene glycol, ammonium hydroxide.

Kalydeco granules
lactose monohydrate, mannitol, hypromellose acetate succinate, croscarmellose sodium, sucralose, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulfate.

What the medicine looks like and contents of the pack
Kalydeco 50 mg granules
white to off-white granules, approximately 2 mm in diameter.

Kalydeco 75 mg granules
white to off-white granules, approximately 2 mm in diameter.

Each of the strengths of Kalydeco granules is available in a pack of 56 sachets. The pack contains 4 individual wallets. Each wallet contains 14 sachets.

Kalydeco 150 mg film-coated tablets
Light blue, capsule shaped, film-coated tablets, printed in black ink with "V 150" on one face and plain on the other.

Kalydeco 150 mg film-coated tablets are available in one of the following packages:
- Blister pack containing 56 film-coated tablets
- Bottle containing 56 film-coated tablets

Registration holder's name and address
Vertex Pharmaceuticals (U.K.) Limited
7 Rival Street, Tel Aviv-Yafo, Israel

Manufacturer's name and address
Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street, London W2 6BD, United Kingdom

Revised in September 2021 according to MOH guidelines.

Registration numbers of the medicine in the Ministry of Health's National Drug Registry
Kalydeco 50 mg granules: 159-08-35051
Kalydeco 75 mg granules: 159-09-35052
Kalydeco 150 mg film coated tablets: 153-89-34269