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

Trikafta 100mg/50mg/75mg & 150mg
Film-coated tablets

Active ingredients and their quantities
Orange film-coated tablets
Each film coated tablet contains elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg.

Light blue film-coated tablets
Each film coated 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 the entire leaflet carefully before you 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 your 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?
Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the CFTR gene or another mutation that is responsive to treatment with Trikafta.

Therapeutic group:
Elexacaftor – CFTR Corrector
Tezacaftor – CFTR Corrector
Ivacaftor – Potentiator of the CFTR protein

Tezacaftor and elexacaftor increase the amount of CFTR protein at the cell surface and ivacaftor causes the protein to work better.

2. Before using the medicine

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

Special warnings about using this medicine

Before taking Trikafta, tell your doctor about all of your medical conditions, including if you:
- have kidney problems
- have or have had liver problems
- are pregnant or plan to become pregnant

- are breastfeeding or planning to breastfeed

Children
Trikafta is not intended for use in children under 12 years of age.

Tests and follow-up
Your doctor will do blood tests to check your liver function:
- before you start taking Trikafta
- every 3 months during your first year of taking Trikafta
- then every year while you are taking Trikafta

Your doctor may do blood tests to check the liver function more often if you have had high liver enzymes in your blood in the past.

Abnormality of the eye lens (cataract) has been noted in some adolescents treated with Trikafta. If you are an adolescent, your doctor should perform eye examinations before and during treatment with Trikafta to look for cataracts.

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

Do not take Trikafta if you are taking:
- rifampin or rifabutin – antibiotic medicines used for treatment of infections
- phenobarbital, carbamazepine, or phenytoin – epileptic seizure medicines
- Hypericum perforatum (St. John's wort) – medicine produced from a plant used for treatment of depression

Talk to your doctor before taking Trikafta if you take any of the medicines listed above.

Trikafta may affect the way other medicines work, and other medicines may affect how Trikafta works. The dose of Trikafta may need to be adjusted when taken with certain medicines. Especially tell your doctor if you take:
- Ketoconazole, itraconazole, posaconazole, voriconazole, or fluconazole – antifungal medicines used for the treatment of fungal infections
- Telithromycin, clarithromycin, or erythromycin – antibiotics used for the treatment of bacterial infections
- Cyclosporine, tacrolimus, everolimus, or sirolimus – immunosuppressants
- Digoxin – cardiac glycoside used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation
- Warfarin – anticoagulant medicine used to prevent blood clots from forming
- Glimepiride, glipizide, glyburide, nateglinide or repaglinide – medicines for diabetes used to lower blood sugar levels
- Statins – lipid-lowering medicines

Using this medicine and food
Avoid food or drink containing grapefruit during treatment with Trikafta as they may increase the amount of elexacaftor, tezacaftor and ivacaftor in your body. **Always take Trikafta with food that contains fat**. Examples of fat-containing foods include butter, peanut butter, eggs, nuts, meat, and whole-milk dairy products such as whole milk, cheese and yogurt.

Pregnancy and breastfeeding
If you are pregnant or think that you are pregnant, planning to have a child or are breast-feeding, consult a doctor or pharmacist before using the medicine. There is limited information on the use of Trikafta in pregnant woman. The doctor will help you decide what is best for you.

It is unknown whether elexacaftor, tezacaftor, or ivacaftor (the active ingredients in Trikafta) are secreted in mother's milk. If you are planning to breastfeed, consult a doctor before taking Trikafta. Your doctor will decide whether to recommend that you stop breast-feeding or for you to stop elexacaftor/tezacaftor/ivacaftor therapy.

Driving and using machines
Trikafta can cause dizziness in some people who take it. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how Trikafta affects you.

Important information about some of this medicine's ingredients
Trikafta's light blue tablet contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to use this medicine

Always use this medicine exactly as your doctor has told you. 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 2 orange tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning and 1 light blue tablet (ivacaftor 150 mg) in the evening.
- Take the orange tablets and the light blue tablet about 12 hours apart.
- Swallow the tablets whole. There is no information about crushing, splitting, or chewing the tablets.

If you have liver problems, your doctor may need to reduce the dose as your liver is not clearing Trikafta as fast as in people who do not have moderate problems with liver function.

Do not exceed the recommended dose.

If you have accidentally taken a higher dosage
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 forgot to take the medicine at the scheduled time:

- If it is **6 hours or less** from the time you usually take the orange tablets in the morning or the light blue tablet in the evening, **take the missed dose** with food that contains fat as soon as you can. Then take your next dose at your usual time.
- If it is **more than 6 hours** from the time you usually take the orange tablets in the morning, **take the missed dose** with food that contains fat as soon as you can. **Do not take the light blue tablet** in the evening.
- If it is **more than 6 hours** from the time you usually take the light blue tablet in the evening, **do not take the missed dose**. Take your next dose of orange tablets at the usual time with food that contains fat.
- Do not take more than your usual dose of Trikafta to make up for a missed 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 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 dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

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

Serious side effects include:

- Liver damage and worsening liver function in people with severe liver disease that can be serious and may require transplantation. Liver damage has also happened in people without liver disease.
- Raised levels of liver enzymes in the blood. It may be a sign of liver injury.
- Abnormality of the eye lens (cataract)

Consult your doctor immediately if you have any of the following symptoms, which may be a sign of liver problems:

- Pain or discomfort in the upper right stomach area
- Yellowing of your skin or the white part of your eyes
- Loss of appetite
- Nausea or vomiting
- Dark, amber-colored urine

<u>Very common side effects (occur in more than one in ten users)</u>

- headache
- upper respiratory tract infection (common cold) including stuffy and runny nose
- stomach (abdominal) pain
- diarrhea

- rash
- increase in liver enzymes

Common side effects (occur in 1-10 in 100 users)
- nasal congestion
- increased creatine phosphokinase (sign of muscle breakdown) seen in blood tests
- stuffy or runny nose
- flu
- sinusitis
- increase in blood bilirubin
- flatulence
- abdominal distension
- conjunctivitis
- pharyngitis
- respiratory tract infection
- tonsillitis
- urinary tract infection
- increase in c-reactive protein
- low blood sugar (hypoglycemia)
- dizziness
- dysmenorrhea
- acne
- eczema
- pruritus

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.

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 Trikafta after the expiry date (exp. date) which is stated on the carton and blister. The expiry date refers to the last day of that month.

Storage conditions
Store below 25°C.

6. Additional Information

In addition to the active ingredients, this medicine also contains:

Orange film-coated tablets
microcrystalline cellulose, croscarmellose sodium, hypromellose acetate succinate (HPMCAS), Hypromellose (HPMC), magnesium stearate and sodium lauryl sulfate (SLS). The tablet film coat contains opadry orange 20A130036.

Light blue film-coated tablets
microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate (HPMCAS), croscarmellose sodium, magnesium stearate, sodium lauryl sulfate (SLS), and colloidal silicon dioxide. The tablet film coat contains polyvinyl alcohol, titanium dioxide, PEG 3350, talc, FD&C Blue #2/indigo carmine aluminum lake, and carnauba wax. The printing ink contains shellac, iron oxide black, n-Butyl alcohol, propylene glycol and ammonium hydroxide.

What the medicine looks like and contents of the pack
Trikafta consists of 2 different tablets:

- Orange film-coated tablet, debossed with "T100" on one face and plain on the other face, and contains the active ingredients elexacaftor, tezacaftor and ivacaftor.
- Light blue film-coated tablet, printed in black ink with "V 150" on one face and contains the active ingredient ivacaftor.

The package contains 84 film-coated tablets. The tablets are packaged in 4 blisters. Each blister contains 21 tablets (14 elexacaftor, tezacaftor and ivacaftor tablets and 7 ivacaftor tablets).

Registration holder's name and address
Vertex Pharmaceuticals (U.K.) Limited
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Manufacturer's name and address
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28-32 Pembroke Street Upper, Dublin 2, D02EK84

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Registration number of the medicine in the Ministry of Health's National Drug Registry
167-03-36448-99