Package leaflet: Information for the patient

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kaftrio is and what it is used for
2. What you need to know before you take Kaftrio
3. How to take Kaftrio
4. Possible side effects
5. How to store Kaftrio
6. Contents of the pack and other information

1. What Kaftrio is and what it is used for

Kaftrio contains three active substances: ivacaftor, tezacaftor and elexacaftor. The medicine helps lung cells to work better in some patients with cystic fibrosis (CF). CF is an inherited condition in which the lungs and the digestive system can become clogged with thick, sticky mucus.

Kaftrio taken with ivacaftor is for **patients aged 6 years and over who have CF, with at least one *F508del* mutation** in the *CFTR* (*cystic fibrosis transmembrane conductance regulator*) gene. Kaftrio is intended as a long-term treatment.

Kaftrio works on a protein called CFTR. The protein is damaged in some people with CF, if they have a mutation in the *CFTR* gene.

Kaftrio is normally taken with another medicine, ivacaftor. Ivacaftor causes the protein to work better, while tezacaftor and elexacaftor increase the amount of protein at the cell surface.

Kaftrio (taken with ivacaftor) helps your breathing by improving your lung function. You may also notice that you do not get ill as often, or that it is easier to gain weight.

2. What you need to know before you take Kaftrio

Do not take Kaftrio:
- **If you are allergic** to ivacaftor, tezacaftor, elexacaftor, or any other ingredients of this medicine (listed in section 6).

Talk to your doctor and do not take the tablets, if this applies to you.

Warnings and precautions

- **Talk to your doctor if you have liver problems** or have had them previously. Your doctor may need to adjust your dose.
- Your doctor will do some **blood tests to check your liver** before and during treatment with Kaftrio, especially if your blood tests showed high liver enzymes in the past. Liver enzymes in the blood can increase in patients receiving Kaftrio.

Tell your doctor right away if you have any symptoms of liver problems. These are listed in section 4.

- **Talk to your doctor** as soon as possible if you (or someone taking this medicine) experience **low mood or any other changes in mood and behaviour**.
  - Effects on mood and behaviour have been reported in patients while taking Kaftrio, usually starting within the first three months of treatment.
  - Symptoms may include anxiety, low or altered mood, and problems with sleep, concentration or forgetfulness.
  - Some children, while taking Kaftrio, may consistently display behaviours that are different to their usual patterns. This could include being more disruptive or difficult to manage.

- **Talk to your doctor if you have kidney problems,** or you have previously had them.

- **Talk to your doctor** before starting treatment with Kaftrio if you have received **an organ transplant**.

- **Talk to your doctor** if you are using hormonal contraception – for example, women using the contraceptive pill. This may mean you are more likely to get a rash while taking Kaftrio.

- **Your doctor may do eye examinations** before and during treatment with Kaftrio. Cloudiness of the eye lens (cataract) without any effect on vision has occurred in some children and adolescents receiving this treatment.

Children under 6

Do not give this medicine to children under the age of 6 years because it is not known if Kaftrio tablets are safe and effective in this age group.

Other medicines and Kaftrio

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Some medicines can affect how Kaftrio works or may make side effects more likely. In particular, tell your doctor if you take any of the medicines listed below. Your doctor may change the dose of one of the medicines if you take any of these.

- **Antifungal medicines** (used for the treatment of fungal infections). These include fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole.
- **Antibiotic medicines** (used for the treatment of bacterial infections). These include clarithromycin, erythromycin, rifampicin, rifabutin, and telithromycin.
- **Epilepsy medicines** (used for the treatment of epileptic seizures or fits). These include carbamazepine, phenobarbital, and phenytoin.
- **Herbal medicines.** These include St. John's wort (*Hypericum perforatum*).
- **Immunosuppressants** (used after an organ transplantation). These include ciclosporin, everolimus, sirolimus, and tacrolimus.
- **Cardiac glycosides** (used for the treatment of some heart conditions). These include digoxin.
- **Anticoagulant medicines** (used to prevent blood clots). These include warfarin.

- **Medicines for diabetes.** These include glimepiride, glipizide, glyburide, nateglinide, and repaglinide.
- **Medicines for lowering blood cholesterol.** These include pitavastatin, and rosuvastatin.
- **Medicines for lowering blood pressure.** These include verapamil.

Kaftrio with food and drink
Avoid food or drinks containing grapefruit during treatment as these may increase the side effects of Kaftrio by increasing the amount of Kaftrio in your body.

Pregnancy and breast-feeding
- **Ask your doctor for advice** before taking this medicine if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.
  - **Pregnancy:** It may be better to avoid using this medicine during pregnancy. Your doctor will help you decide what is best for you and your child.
  - **Breast-feeding:** It is not known if ivacaftor, tezacaftor or elexacaftor passes into breast milk. Your doctor will consider the benefit of breast-feeding for your baby and the benefit of treatment for you to help you decide whether to stop breast-feeding or to stop treatment.

Driving and using machines
Kaftrio can make you dizzy. If you feel dizzy, do not drive, cycle, or use machines unless you are not affected.

Kaftrio contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

3. How to take Kaftrio

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

There are different strengths of Kaftrio for different age groups. Check you have been given the right dose (below).
Kaftrio is usually taken with ivacaftor.

Recommended dose for patients aged 6 years and over:

Age	Weight	Morning Dose	Evening Dose
6 to <12 years	<30 kg	Two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets	One ivacaftor 75 mg tablet
6 to <12 years	≥30 kg	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet
≥12 years	-	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet

Take the morning and evening tablets about 12 hours apart.

The tablets are for oral use.

Take both Kaftrio and ivacaftor tablets with food that contains fat. 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

Avoid food and drink containing grapefruit while you are taking Kaftrio. See *Kaftrio with food and drink* in section 2 for more details.

Swallow the tablets whole. Do not chew, crush or break the tablets before swallowing.

You must keep using all your other medicines, unless your doctor tells you to stop.

If you have liver problems, either moderate or severe, your doctor may reduce the dose of your tablets or decide to stop treatment with Kaftrio. See also *Warnings and precautions* in section 2.

If you take more Kaftrio than you should
Contact your doctor or pharmacist for advice. If possible, take your medicine and this leaflet with you. You may get side effects, including those mentioned in section 4 below.

If you forget to take Kaftrio
If you forget a dose, work out how long it is since the dose you missed.

- **If less than 6 hours** have passed since you missed a dose, either morning or evening, take the forgotten tablet(s) as soon as possible. Then go back to your usual schedule.
- **If more than 6 hours** have passed:
  - **If you missed a morning dose** of Kaftrio, take it as soon as you remember. Do not take the evening dose of ivacaftor. Take the next morning dose at the usual time.
  - **If you missed an evening** dose of ivacaftor, do not take the missed dose. Wait for the next day and take the morning dose of Kaftrio tablets as usual.

Do not take a double dose to make up for any missed tablets.

If you stop taking Kaftrio
Your doctor will tell you how long you need to keep taking Kaftrio. It is important to take this medicine regularly. Do not make changes unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects:

Possible signs of liver problems
Liver damage and worsening of liver function in people with or without liver disease. The worsening of liver function can be serious and may require transplantation.

Increased liver enzymes in the blood are very common in patients treated with Kaftrio. These may be signs of liver problems:

- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Tell your doctor straight away if you have any of these symptoms.

Very common side effects (may affect more than 1 in 10 people)
- Rash (more common in women than in men)

Tell your doctor straight away if you notice a rash.

Other side effects:
Very common (may affect more than 1 in 10 people)
- Headache
- Dizziness
- Upper respiratory tract infection (common cold)
- Oropharyngeal pain (sore throat)
- Nasal congestion
- Stomach or abdominal pain
- Diarrhoea
- Increased liver enzymes (signs of stress on the liver)
- Changes in the type of bacteria in mucus
- Increased creatine phosphokinase (sign of muscle breakdown) seen in blood tests

Common (may affect up to 1 in 10 people)
- Flu
- Abnormal breathing (Shortness of breath or difficulty breathing)
- Low blood sugar (hypoglycaemia)
- Runny nose
- Sinus problems (sinus congestion)
- Redness or soreness in the throat
- Ear problems: ear pain or discomfort, ringing in the ears, inflamed eardrum
- Spinning sensation (inner ear disorder)
- Wind (flatulence)
- Spots (acne)
- Itchy skin
- Breast mass
- Feeling nauseous

Uncommon (may affect up to 1 in 100 people)
- Breast and nipple problems: inflammation, pain
- Enlargement of the breast in men
- Increases in blood pressure
- Wheezing
- Blocked ears (ear congestion)

Not known (frequency cannot be estimated from the available data)
- Damage to the liver (liver injury)
- Raised bilirubin measurement (liver blood test)
- Low mood. Signs of this can include changes in behaviour in children

Additional side effects in adolescents
Side effects in adolescents are similar to those observed in adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kaftrio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Kaftrio contains
- The active substances are ivacaftor, tezacaftor and elexacaftor.

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
Each film-coated tablet contains 37.5 mg of ivacaftor, 25 mg of tezacaftor and 50 mg elexacaftor.

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
Each film-coated tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg elexacaftor.

- The other ingredients are:
  - Tablet core: Hypromellose (E464), hypromellose acetate succinate, sodium laurilsulfate (E487), croscarmellose sodium (E468), microcrystalline cellulose (E460(i)), and magnesium stearate (E470b).
  - Tablet film coating: Hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), and iron oxide red (E172).

See the end of section 2 for important information about the contents of Kaftrio.

What Kaftrio looks like and contents of the pack
Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets are light orange, capsule-shaped tablets stamped with “T50” on one side and plain on the other.

Kaftrio 75 mg/50 mg/100 mg film-coated tablets are orange, capsule-shaped tablets stamped with “T100” on one side and plain on the other.

Kaftrio is available in pack size of 56 tablets (4 blister cards, each with 14 tablets).

Marketing Authorisation Holder
Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London, W2 6BD
United Kingdom
Tel: +44 (0)203 204-5100

Manufacturer
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

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Other sources of information
Detailed information on this medicine is available on the website of Medicines and Healthcare products Regulatory Agency: http://www.mhra.gov.uk.