

Kaftrio® ▼ (ivacaftor/tezacaftor/elexacaftor) Prescribing Information (IRE)
(Refer to the Summary of Product Characteristics for full information)

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

Presentations: Film-coated tablet containing 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

Therapeutic Indications: Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation.

Dosage and Administration: Kaftrio should only be prescribed by physicians with experience in the treatment of CF. If the patient's genotype is unknown, confirm the presence of two *F508del* mutations or the presence of one *F508del* mutation and a minimal function mutation using a genotyping assay. Recommended dose for ≥ 12 years: two Kaftrio tablets in the morning and one ivacaftor 150 mg tablet in the evening, approximately 12 hours apart. A dose adjustment is recommended when co-administered with moderate/strong CYP3A inhibitors. Treatment of patients with moderate hepatic impairment is not recommended and should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose. Patients with severe hepatic impairment should not be treated with Kaftrio. **Administration:** For oral use. Kaftrio should be taken with fat-containing food. Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, crushed, or broken before swallowing.

Contraindications: Hypersensitivity to the active substance(s) or to any of the excipients.

Special Warnings and Precautions: Effect on liver function tests: Elevated transaminases have been observed in some patients treated with Kaftrio in combination with ivacaftor. Assessments of transaminases are recommended for all patients prior to initiating treatment, every 3 months during the first year, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x the ULN, or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered. Hepatic impairment: Treatment of patients with moderate hepatic impairment is not recommended. Patients with severe hepatic impairment should not be treated with Kaftrio. Renal impairment: Caution is recommended while using Kaftrio in combination with ivacaftor in patients with severe renal impairment or end-stage renal disease. Patients after organ transplantation: Use of Kaftrio in combination with ivacaftor in transplanted patients is not recommended. Rash events: The incidence of rash events was higher in females than in males, particularly in females taking hormonal contraceptives. A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, interrupting treatment with Kaftrio in combination with ivacaftor and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming Kaftrio in combination with ivacaftor without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered. Elderly population: Clinical studies of Kaftrio in combination with ivacaftor did not include any patients over 59 years of age. Dose recommendations are based on the pharmacokinetic profile and knowledge from studies with tezacaftor/ivacaftor in combination with ivacaftor and ivacaftor monotherapy. Interactions with medicinal products: *CYP3A inducers and CYP3A inhibitors:* see Pharmacokinetic Interactions. Cataracts: Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up

ophthalmological examinations are recommended in paediatric patients initiating treatment with Kaftrio in combination with ivacaftor. **Sodium content:** This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Pharmacokinetic Interactions: *CYP3A inducers:* Co-administration with strong CYP3A inducers is not recommended. *CYP3A inhibitors:* The dose of Kaftrio and ivacaftor should be reduced when co-administered with strong or moderate CYP3A inhibitors. Food or drink containing grapefruit should be avoided during treatment with Kaftrio and ivacaftor. *Transporters:* Caution should be used when P-gp inhibitors are used with Kaftrio. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as ciclosporin, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used. Bilirubin is an OATP1B1 and OATP1B3 substrate. Mild increases in mean total bilirubin were observed in study 445-102 consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by elexacaftor and M23-ELX. When used concomitantly with substrates of BCRP, appropriate monitoring should be used. *CYP2C9 substrates:* Monitoring of the international normalized ratio (INR) during co-administration of warfarin with Kaftrio and ivacaftor is recommended. CYP2C9 substrates such as glimepiride and glipizide should be used with caution. *Hormonal contraceptives:* Kaftrio and ivacaftor is not expected to have an impact on the efficacy of oral contraceptives.

Pregnancy and breast-feeding: **Pregnancy:** As a precautionary measure, it is preferable to avoid the use of Kaftrio during pregnancy. **Breast-feeding:** A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kaftrio therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **Fertility:** No data available on the effect of elexacaftor, tezacaftor and ivacaftor on fertility in humans. Elexacaftor and ivacaftor had an effect on fertility in rats.

Effects on ability to drive and use machines: Patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

Undesirable Effects: Most common adverse reactions experienced by patients aged ≥ 12 years with Kaftrio in combination with ivacaftor were headache (17.3%), diarrhoea (12.9%) and upper respiratory tract infection (11.9%). Serious adverse reactions of rash were reported in 3 (1.5%) patients treated with Kaftrio in combination with ivacaftor compared to 1 (0.5%) in placebo. Adverse reactions observed with Kaftrio in combination with ivacaftor, tezacaftor/ivacaftor in combination with ivacaftor and ivacaftor monotherapy: very common ($\geq 1/10$): upper respiratory tract infection, nasopharyngitis, headache, dizziness, oropharyngeal pain, nasal congestion, diarrhoea, abdominal pain, transaminase elevations, rash, bacteria in sputum; common ($\geq 1/100$ to $< 1/10$): rhinitis, influenza, hypoglycaemia, ear pain, ear discomfort, tinnitus, tympanic membrane hyperaemia, vestibular disorder, rhinorrhoea, sinus congestion, pharyngeal erythema, abnormal breathing, nausea, abdominal pain upper, flatulence, alanine aminotransferase increased, aspartate aminotransferase increased, acne, pruritus, breast mass, blood creatine phosphokinase increased; uncommon ($\geq 1/1,000$ to $< 1/100$): ear congestion, wheezing, breast inflammation, gynaecomastia, nipple disorder, nipple pain, blood pressure increased.

Legal Category: POM, prescription-only medicine.

Price information: €9,819.18 per 28-day pack containing 56 ivacaftor 75mg /tezacaftor 50mg /elexacaftor 100mg fixed dose combination tablets

Marketing Authorisation Holder: Vertex Pharmaceuticals (Ireland) Limited, 28-32 Pembroke Street Upper, Dublin 2, D02 EK84, Ireland.

Marketing Authorisation Numbers: EU/1/20/1468/001.

Date of Revision of the Text: August 2020.

Kafrio is a trademark of Vertex Pharmaceuticals Incorporated, from whom further information is available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse events should be reported. Reporting forms and information can be found at HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

**Adverse events should also be reported to
Vertex Pharmaceuticals (Ireland) Ltd 1800 924 568 or +353 (0)1 761 7299**