

Summary of Risk Management Plan for KAFTRIO (Elexacaftor in Combination With Tezacaftor and Ivacaftor)

This is a summary of the risk management plan (RMP) for KAFTRIO when used in a combination regimen with ivacaftor 150 mg tablets. The RMP details important risks of KAFTRIO, how these risks can be minimised, and how more information will be obtained about KAFTRIO's risks and uncertainties (missing information) when used in combination with ivacaftor.

KAFTRIO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KAFTRIO should be used.

This summary of the RMP for KAFTRIO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current ones will be included in updates of KAFTRIO's RMP.

I. The medicine and what it is used for

KAFTRIO in a combination regimen with ivacaftor (150 mg tablets) is authorised for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the CF transmembrane conductance regulator (*CFTR*) gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function mutation (see SmPC for the full indication). It contains elexacaftor in combination with tezacaftor and ivacaftor as the active substances and it is given orally.

Further information about the evaluation of KAFTRIO's benefits when used in combination with ivacaftor can be found in KAFTRIO's EPAR, including its plain-language summary, available on the EMA website under the medicine's webpage:

<https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of KAFTRIO when used in combination with ivacaftor, together with measures to minimise such risks and the proposed studies for learning more about KAFTRIO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of KAFTRIO in combination with ivacaftor is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of KAFTRIO in combination with ivacaftor are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of KAFTRIO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	<ul style="list-style-type: none"> • Susceptibility for influenza virus infections
Important potential risks	<ul style="list-style-type: none"> • Hepatotoxicity • Cataract
Missing information	<ul style="list-style-type: none"> • Use in pregnant and lactating women • Long-term safety • Use in patients with moderate or severe hepatic impairment

II.B Summary of important risks

Susceptibility for influenza virus infections (Important identified risk)	
Evidence for linking the risk to the medicine	<p>In the 24-week, placebo-controlled Phase 3 study in CF subjects 12 years of age and older (Study 102), a higher incidence of influenza AEs was reported in the ELX/TEZ/IVA group compared to the placebo group. In the KAFTRIO (ELX/TEZ/IVA) group, all AEs of influenza were mild or moderate in severity and most were non-serious. All subjects continued KAFTRIO (ELX/TEZ/IVA) dosing or resumed treatment after an interruption. In the open-label extension Study 105, the rate of influenza AEs during extended KAFTRIO (ELX/TEZ/IVA) treatment was lower than the rate in the KAFTRIO (ELX/TEZ/IVA) group in Study 102, and similar to the rate in the placebo group in Study 102.</p> <p>Based on the overall safety experience with KAFTRIO (ELX/TEZ/IVA), an association between treatment and the susceptibility for influenza cannot be completely excluded.</p>
Risk factors and risk groups	<p>Patients who are hospitalised frequently or for long-term durations are at a greater risk for contracting influenza from other infected individuals. Risk factors for influenza-related complications include common CF comorbidities (e.g., chronic lung disease, asthma) and a compromised immune system.</p>
Risk minimisation measures	<p>SmPC Sections 4.8 PL Section 4 Prescription only</p>
Additional pharmacovigilance activities	<ul style="list-style-type: none"> • Open-label extension study (Study 105) • Post-authorisation safety study <p>See Section II.C of this summary for an overview of the post-authorisation development plan.</p>

Hepatotoxicity (Important potential risk)

Evidence for linking the risk to the medicine	<p>In the 24-week, placebo-controlled, Phase 3 study in CF subjects 12 years of age and older (Study 102), the incidence of elevated transaminase events (AEs or ALT/AST laboratory elevations $>3 \times$ ULN) was higher in the group of subjects treated with KAFTRIO (ELX/TEZ/IVA) than in the group of subjects receiving placebo. LFT elevations were also seen in other clinical studies with KAFTRIO (ELX/TEZ/IVA), including the open-label extension study (Study 105).</p> <p>Elevated transaminases with KAFTRIO (ELX/TEZ/IVA) treatment were generally transient and resolved without long-term effects. Very high levels of transaminase elevations or transaminase elevations with concurrent total bilirubin elevation may be a sign of liver injury which could become permanent or be life-threatening. The overall safety experience with KAFTRIO (ELX/TEZ/IVA) does not suggest a causal association between treatment and hepatotoxicity; however, the potential for hepatotoxicity cannot be excluded.</p>
Risk factors and risk groups	Generally known risk factors for increases in transaminases include concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, viral hepatitis), comorbidities (e.g., CF liver disease), and use of concomitant drugs (e.g., acetaminophen, antibiotics) or substances (alcohol) known to be associated with liver enzyme elevations.
Risk minimisation measures	SmPC Sections 4.4 and 4.8 SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided. PL Sections 2 and 4 PL Sections 2 and 4 where expectations for LFT monitoring and detection of potential signs of liver problems are discussed. Prescription only
Additional pharmacovigilance activities	<ul style="list-style-type: none">• Open-label extension study (Study 105)• Post-authorisation safety study See Section II.C of this summary for an overview of the post-authorisation development plan.

Cataract (Important potential risk)

Evidence for linking the risk to the medicine	<p>Cataracts (lens opacities) considered related to IVA treatment were seen during studies in newborn rats but were not observed in older animals or in longer duration animal studies. Given developmental differences between rats and humans, it is unlikely that the cataract finding is relevant to humans 12 years of age and older.</p> <p>Non-congenital cataracts without impact on vision have been reported in paediatric subjects treated with IVA-containing regimens during clinical studies and post-authorisation surveillance, but the relationship of these events to treatment is uncertain due to the presence of other possible causes.</p>
Risk factors and risk groups	Risk factors for cataracts include aging, trauma, UV light and radiation exposure, diabetes mellitus, intraocular inflammation, and corticosteroid use.
Risk minimisation measures	SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided. PL Section 2 PL Section 2 where expectations for eye examinations are discussed. Prescription only
Additional pharmacovigilance activities	<ul style="list-style-type: none">• Open-label extension study (Study 105) See Section II.C this summary for an overview of the post-authorisation development plan.

Use in pregnant and lactating women (Missing information)

Risk minimisation measures	SmPC Sections 4.6 and 5.3 SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding. PL Section 2 PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding. Prescription only
Additional pharmacovigilance activities	<ul style="list-style-type: none">• Post-authorisation safety study See Section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety (Missing information)	
Risk minimisation measures	SmPC Section 4.8 Prescription only
Additional pharmacovigilance activities	<ul style="list-style-type: none"> • Open-label extension study (Study 105) • Post-authorisation safety study See Section II.C of this summary for an overview of the post-authorisation development plan.
Use in patients with moderate or severe hepatic impairment (Missing information)	
Risk minimisation measures	SmPC Sections 4.2, 4.4, and 5.2 SmPC Sections 4.2 and 4.4 where recommendations regarding use in patients with hepatic impairment are provided. PL Sections 2 and 3 PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided. Prescription only
Additional pharmacovigilance activities	<ul style="list-style-type: none"> • Study in patients with moderate hepatic impairment (Study 007) (for evaluation of use in patients with moderate hepatic impairment only) • Post-authorisation safety study See Section II.C of this summary for an overview of the post-authorisation development plan.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor (also known as KAFTRIO); IVA: ivacaftor (a component of KAFTRIO); LFT: liver function test; PL: Package Leaflet; SmPC: Summary of Product Characteristics; Study 007: VX18-445-007; Study 102: VX17-445-102; Study 105: VX17-445-105; ULN: upper limit of normal; UV: ultraviolet

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of KAFTRIO when used in a combination regimen with ivacaftor (150 mg tablets).

II.C.2 Other studies in post-authorisation development plan

Study in patients with moderate hepatic impairment (Study 007)

Purpose of the study: To evaluate the safety, tolerability, and pharmacokinetics of ELX/TEZ/IVA in subjects without CF who have moderate hepatic impairment and in matched healthy subjects

Open-label extension study (Study 105)

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy and the pharmacodynamics of ELX/TEZ/IVA treatment for 96 weeks in subjects 12 years of age and older with CF, homozygous or heterozygous for the *F508del-CFTR* mutation

Post-authorisation safety study (PASS)

Purpose of the study: To evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting