

Summary of Risk Management Plan for Symkevi (tezacaftor/ivacaftor)

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

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

This summary of the RMP for Symkevi used in combination with ivacaftor 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 concerns or changes to the current ones will be included in updates of Symkevi's RMP.

I. The medicine and what it is used for

Symkevi in a combination regimen with ivacaftor tablets is authorised for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T* (see SmPC for the full indication). It contains tezacaftor in combination with ivacaftor as the active substance and it is given orally.

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

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

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

Important risks of Symkevi in combination with ivacaftor, together with measures to minimise such risks and the proposed studies for learning more about Symkevi's risks in a combination with ivacaftor, 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 Symkevi 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 Symkevi 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 Symkevi in combination with ivacaftor. 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"> • None
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 • Patients with moderate or severe hepatic impairment • Patients with ppFEV₁ < 40

ppFEV₁: forced expiratory volume in 1 second

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Hepatotoxicity (important potential risk)	
Evidence for linking the risk to the medicine	Elevations in transaminases are common in patients with CF, and have been observed in some patients treated with TEZ/IVA, as well as with IVA monotherapy. Overall, the incidence of elevated liver function tests (LFTs) were well balanced between the TEZ/IVA or IVA monotherapy groups compared to the placebo group in the placebo-controlled Phase 3 studies. However, in the IVA programme, increased ALT or AST has been reported slightly more frequently in the subset of patients with a medical history of elevated transaminases who received IVA monotherapy, compared to placebo. The potential role of IVA monotherapy or TEZ/IVA is uncertain, and cannot be fully excluded. The data from the open-label extension study in patients 12 years and older are consistent with the placebo-controlled trials.
Risk factors and risk groups	Only generally known risk factors for increases in LFTs were identified in several instances, including concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu like illness, haemoptysis, kidney infection), cystic fibrosis (CF), as well as concomitant drugs (e.g., acetaminophen, antibiotics) and substances (e.g., alcohol) known to be associated with LFT elevations.
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC Sections 4.4 and 4.8 SmPC Section 4.4 and PL Sections 2 and 4 where advice is given on monitoring LFTs PL Sections 2 and 4 Prescription only</p> <p>Additional risk minimisation measures: No risk minimisation measures</p>

Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Study 117 (PASS) <p>See Section II.C of this summary for an overview of the post-authorisation development plan.</p>
Cataract (important potential risk)	
Evidence for linking the risk to the medicine	<p>Lens opacities (cataracts) were observed in newborn rats and were considered related to IVA treatment. This finding has not been observed in older animals. Given species developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 12 years of age and older.</p> <p>There is a high background rate of cataract in patients with CF. The placebo controlled ocular safety data in the TEZ/IVA and IVA clinical development programmes did not suggest any imbalance in cataract incidence between the TEZ/IVA or IVA monotherapy groups compared to the placebo groups. Cases of non-congenital lens opacities were reported in paediatric subjects with TEZ/IVA or IVA monotherapy; these cases involved subtle ophthalmological findings with no impact on visual acuity, and a lack of progression. Although risk factors (e.g., corticosteroid use, exposure to radiation) were present in some cases, a contributing role of TEZ/IVA or IVA monotherapy cannot be completely excluded.</p>
Risk factors and risk groups	Risk factors for cataracts include aging, trauma, ultraviolet light and radiation exposure, diabetes mellitus, intraocular inflammation, CF, and systemic or topical corticosteroid use.
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>SmPC Sections 4.4 and 5.3</p> <p>SmPC Section 4.4 where advice is given on recommended ophthalmological examinations.</p> <p>PL Section 2</p> <p>Prescription only</p> <p>Additional risk minimisation measures:</p> <p>No risk minimisation measures</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>See Section II.C of this summary for an overview of the post-authorisation development plan.</p>
Use in pregnant and lactating women (missing information)	
Risk minimisation measures	<p>SmPC Section 4.6 and 5.3</p> <p>SmPC Section 4.6 and PL Section 2 where advice is given to avoid the use of Symkevi during pregnancy and to determine the use during breastfeeding after taking into account the benefit of breastfeeding the child and the benefit of therapy for the woman.</p> <p>PL Section 2.</p> <p>Prescription only</p>
Additional pharmacovigilance activities	• Study 117 (PASS)
Long-term safety (missing information)	
Risk minimisation measures	<p>SmPC Sections 4.8 and 5.1</p> <p>SmPC Sections 4.8 and 5.1 describe the available clinical evidence, including the number and extent of exposure in clinical studies.</p> <p>Prescription only</p>
Additional pharmacovigilance activities	• Study 117 (PASS)
Patients with moderate or severe hepatic impairment (missing information)	
Risk minimisation measures	<p>SmPC Sections 4.2, 4.4, and 5.2</p> <p>SmPC Section 4.2 where advice is given on dose adjustment based on severity of hepatic impairment.</p> <p>PL Section 3.</p> <p>Prescription only</p>
Additional pharmacovigilance activities	• Study 117 (PASS)
Patients with ppFEV₁ <40 (missing information)	
Risk minimisation measures	<p>SmPC Section 5.1</p> <p>Prescription only</p>
Additional pharmacovigilance activities	• Study 117 (PASS)

ADR: adverse drug reaction; CF: cystic fibrosis; IVA: ivacaftor; LFT: liver function test; PK pharmacokinetics;
PASS: Post-authorisation safety study; PL: Package Leaflet; ppFEV₁: forced expiratory volume in 1 second ;
SmPC: Summary of Product Characteristics; TEZ/IVA: tezacaftor in combination with ivacaftor

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 Symkevi in a combination regimen with ivacaftor tablets.

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

Short study name: Study 117 (PASS)

Purpose of the study: Evaluate the utilisation patterns and real-world effects of TEZ/IVA therapy in patients with CF