CSL Vifor

SUMMARY OF THE RISK MANAGEMENT PLAN (CH) FOR KAPRUVIA® (DIFELIKEFALIN)

Invented Name:	Kapruvia
Active Substance:	Difelikefalin
Current RMP:	EU RMP Version 2.0 dated 23 August 2022 (data lock point 15 May 2020)
Date of the Report:	14 March 2024
Marketing Authorisation Holder:	Vifor Fresenius Medical Care Renal Pharma Ltd. Rechenstrasse 37 9014 St. Gallen Switzerland

Disclaimer

The RMP is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Kapruvia is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/ Information sur le Médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Kapruvia in Switzerland is the "Arzneimittelinformation/Information sur le Médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Vifor Fresenius Medical Care Renal Pharma France is fully responsible for the accuracy and correctness of the content of the published summary RMP of Kapruvia.

Following the acquisition of Vifor Pharma by CSL on 9 August 2022, Vifor Pharma is now operating under the brand CSL Vifor and is a dedicated business unit of CSL. The Vifor Pharma legal entities will continue to use the Vifor Pharma entity names until the appropriate legal and regulatory approvals are obtained.

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SUMMARY OF THE RMP FOR KAPRUVIA (DIFELIKEFALIN)

This is a summary of the Risk Management Plan (RMP) for Kapruvia (hereafter also referred to as difelikefalin). The RMP details important risks of Kapruvia, how these risks can be minimised, and how more information will be obtained about Kapruvia's risks and uncertainties (missing information).

Kapruvia's Swiss Summary of Product Characteristics (Swiss SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Kapruvia should be used.

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

I. The Medicine and What it is Used for

According to Swiss Label

Kapruvia is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

According to EU SmPC

Kapruvia is authorised for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

Further information about the evaluation of Kapruvia's benefits can be found in Kapruvia's European Public Assessment Report (EPAR), including in its plain-language summary, available on the EMA website, under the webpage https://www.ema.europa.eu/en/medicines/human/EPAR/kapruvia.

It contains difelikefalin as the active substance and is given as 50 micrograms/ml solution for injection.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Kapruvia, together with measures to minimise such risks and the proposed studies for learning more information about Kapruvia'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 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.

In addition to these measures, information about adverse reactions is collected continuously and in an enhanced manner using specific follow-up Target Questionnaires, and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that can affect the safe use of Kapruvia is not yet available, it is listed under missing information below.

II.A List of Important Risks and Missing Information

Important risks of Kapruvia are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Kapruvia. 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	None
Important potential risks	Cardiac failure and arrhythmias including atrial fibrillation in haemodialysis patients with a medical history of atrial fibrillation
Missing information	Use in pregnant and lactating women Use in patients with impaired blood brain barrier Use in patients with severe hepatic impairment

II.B Summary of Important Risks

Important Potential Risk: Cardiac failure and arrhythmias including atrial fibrillation in HD patients with a medical history of AF	
Evidence for linking the risk to the medicine	There is currently insufficient evidence to conclude a causal association between cardiac events (including AF in HD patient with a medical history of AF) and difelikefalin administration. Data from Phase 3 interventional studies showed small numerical differences in serious events of cardiac failure and cardiac arrhythmias and numerically increased relative risk TEAEs in the Cardiac Disorders SOC in subjects with a medical history of AF that disfavoured difelikefalin compared to placebo.
Risk factors and risk groups	CKD patients undergoing HD have a markedly increased cardiovascular risk, which is likely to be further impacted by CKD-aP. Clinical data shows that there is inadequate evidence of an association with difelikefalin and an increased risk of cardiac related events in subjects with CKD-aP undergoing HD, including HD subjects with a medical history of AF. Based on a quantitative analysis, there was a numerically increased relative risk (difelikefalin versus placebo) of TEAEs in the Cardiac Disorders SOC in subjects with a medical history of AF. There was no other subgroup of subjects identified with increased susceptibility to serious cardiac TEAEs with difelikefalin use. No other clinically important pre-existing risk factors (e.g., age, gender, race and medical history of cardiac failure, hypertension, or hyperkalaemia) were identified from the clinical trial population.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None
Missing Information: Use in pregnant or lactating women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6; PIL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None
Missing Information: Use in patients with impaired blood brain barrier	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PIL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None
Missing Information: Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2; PIL Section 3 • Legal status: Prescription only medicine Additional risk minimisation measures: None

Notes: AF=Atrial fibrillation; CKD=Chronic kidney disease; CKD-aP=Chronic kidney disease–associated pruritus; HD=Haemodialysis; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics; SOC=System organ class; TEAE=Treatment-emergent adverse event.

II.C Post-authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or a specific obligation for Kapruvia.

II.C.2 Other Studies in Post-authorisation Development Plan

CR845-310301

A Multicentre, Randomized, Double-blind, Placebo-controlled 12-Week Study to Evaluate the Safety and Efficacy of Oral Difelikefalin in Advanced Chronic Kidney Disease Subjects with Moderate-to-Severe Pruritus and not on Dialysis with an up to 52-Week Long-term Extension.

CR845-310302

A Multicentre, Randomized, Double-blind, Placebo-controlled 12-Week Study to Evaluate the Safety and Efficacy of Oral Difelikefalin in Advanced Chronic Kidney Disease Subjects with Moderate-to-Severe Pruritus and not on Dialysis with an up to 52-Week Long-term Extension.

Phase 3 Study in Adult Subjects with Atopic Dermatitis (Study Identifier to be Updated)

Phase 3: A Two-part, Multicentre, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Oral Difelikefalin as Adjunct Therapy to a Topical Corticosteroid for Moderate-to-Severe Pruritus in Adult Subjects with Atopic Dermatitis.