Swiss Summary of the Risk Management Plan (RMP) for Fruquintinib (Fruzaqla)

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Marketing Authorization Holder: Takeda Pharma AG

The Risk Management Plan (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 risk as well as to prevent or minimise them.

The RMP summary of Fruzaqla 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 authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Fruzaqla in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Fruzaqla.

Summary of risk management plan for FRUZAQLA (Fruquintinib)

This is a summary of the risk management plan (RMP) for FRUZAQLA. The RMP details important risks of FRUZAQLA's and how more information will be obtained about FRUZAQLA's risks and uncertainties (missing information).

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

This summary of the RMP for FRUZAQLA 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 FRUZAQLA's RMP.

I. The medicine and what it is used for

FRUZAQLA as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib (see SmPC for the full indication). It contains fruquintinib as the active substance and it is given orally as 1 mg or 5 mg hard capsule.

Fruzaqla's benefits can be found in Fruzaqla's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of FRUZAQLA 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 FRUZAQLA. 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	Haemorrhage Hypertension Posterior reversible encephalopathy syndrome (PRES) Gastrointestinal perforation Palmar-plantar erythrodysaesthesia syndrome (PPES) Proteinuria
Important potential risks	Arterial thromboembolic events Impaired wound healing Aneurysms and artery dissections
Missing information	Safety in ethnicities other than Asian and White

II.B Summary of important risks and missing information

Important Identified Risk: Haemorrhage	
Evidence for linking the risk to the medicine	Fruquintinib clinical trials and post-marketing reports (China).
Risk factors and risk groups	Patients may be at increased risk of hemorrhage when taking concomitant antiplatelet, anticoagulant, antithrombotic or other drugs that have been associated with an increased risk of hemorrhage. Patients with tumor invasion in the digestive tract before the administration of fruquintinib may be at increased risk of gastrointestinal haemorrhage.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None

Additional pharmacovigilance activities	None

Important Identified Risk: Hypertension	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo) and ISAS Expanded mCRC data.
Risk factors and risk groups	Known history of uncontrolled hypertension. Clinically significant cardiovascular disease. Comorbidities such as diabetes mellitus, ischemic heart disease, etc.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo) and ISAS Expanded mCRC data.
Risk factors and risk groups	Uncontrolled hypertension, chronic renal failure
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Gastrointestinal perforation	
Evidence for linking the	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo)

risk to the medicine	and ISAS Expanded mCRC data.
Risk factors and risk groups	Comorbidities such as diffuse abdominal carcinomatosis associated with a risk of bowel obstruction, increased pressure on weakened bowel areas and microperforations. Other risk factors include ulcer, bowel tumor necrosis, diverticulosis, colitis and prior abdominal or pelvic radiotherapy.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Palmar-plantar erythrodysaesthesia syndrome (PPES)	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo) and ISAS Expanded mCRC data.
Risk factors and risk groups	Higher rates of toxicity were noted in Asian patients compared with historical cohorts in clinical trials. For example, the incidence of hand-foot syndrome (55% in a Japanese study vs 30% in the initial landmark phase III study. As class of agents, VEGFR inhibitors are known to cause PPES. PPES or HFS has been reported to occur between Days 14 and 28 of VEGF inhibitor treatment.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Proteinuria	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo) and ISAS Expanded mCRC data.
Risk factors and risk	Pre-existing proteinuria and in patients with renal cell

groups	carcinoma (RCC) using VEGF inhibitors such as axitinib were significantly associated in patients developing Grade >2 proteinuria.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Potential Risk: Arterial thromboembolic events	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo) and ISAS.
Risk factors and risk groups	Multiple risk factors increase the risk of thromboembolic events in patients with cancer, including cancer-associated hypercoagulable state, older age, advanced stage, prolonged immobilization, chemotherapy, vessel stasis from direct tumor compression, frequent hospitalization and surgery. Endothelial dysfunction in the presence of VEGF inhibition may predispose patients to thrombosis, with arterial events generally the more observed than venous.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Potential Risk: Impaired wound healing	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo) and ISAS.
Risk factors and risk groups	Hypoxia is one reason VEGF increases during wound healing.

Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Important Potential Risk: Aneurysms and artery dissections	
Evidence for linking the risk to the medicine	Pooled ISAS monotherapy mCRC data (fruquintinib vs placebo), ISAS, and Study 2018-013-00CH2.
Risk factors and risk groups	Hypertension and history of aneurysm.
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Missing Information: Safety in ethnicities other than Asian and White	
Risk minimization measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

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 FRUZAQLA.

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

TAK-113-4002: A Single Arm Phase 4 Study to Evaluate the Safety and Efficacy of Oral Fruquintinib in the Treatment of Refractory Metastatic Colorectal Cancer in Patients from Underrepresented Minority Populations.

Purpose of the study: The primary objective is to determine the incidence of Grade 3 and Grade 4 hypertension in underrepresented minority patients (Black/African American and/or Hispanic/Latino) treated with fruquintinib for refractory mCRC.

The secondary objectives are:

- To assess additional safety and tolerability of fruquintinib.
- To evaluate the OS of patients treated with fruquintinib.
- To evaluate the PFS of patients treated with fruquintinib.
- To evaluate the objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) in patients treated with fruquintinib.
- To characterize the PK of fruquintinib.