Date: 1 November 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Fruzaqla

International non-proprietary name: fruquintinib
Pharmaceutical form: hard capsules
Dosage strength(s): 1 mg, 5 mg
Route(s) of administration: oral
Marketing authorisation holder: Takeda Pharma AG
Marketing authorisation no.: 69524
Decision and decision date: approved on 27 August 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCS	Biopharmaceutics classification system
BSC	Best supportive care
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CRC	Colorectal cancer
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ER	Exposure-response
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
mCRC	Metastatic colorectal cancer
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily

RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TAS-102	Trifluridine/tipiracil
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for fruquintinib in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia, Canada, Singapore, and the UK.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy or are not considered candidates for available therapies.

2.2.2 Approved indication

Fruzaqla is used as monotherapy 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 chemotherapy, an anti-VEGF agent, and, in the presence of wild-type RAS, with an anti-EGFR agent, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is 5 mg orally once daily and can be taken with or without food for the first 21 days of each 28-day cycle.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	29 September 2023
Formal control completed	29 October 2023
List of Questions (LoQ)	26 February 2024
Response to LoQ	25 April 2024
Preliminary decision	10 June 2024
Response to preliminary decision	24 June 2024
Labelling corrections	24 July 2024
Response to labelling corrections	19 August 2024
Final decision	27 August 2024
Decision	approval

3 Medical context

Colorectal cancer (CRC) is the third most common cancer worldwide and occurs more frequently in middle- to high-income countries (Sung, 2021); in Europe in 2018, CRC accounted for the second highest number of cancer deaths (Malvezzi, 2018). In Switzerland CRC has an incidence of 54 per 100,000 person-years, and incidence is higher in men than in women (61 vs 45 per 100,000 person-years) (NKRS Statistiken, 2015-2019).

Approximately 15%-30% of patients have metastases at diagnosis, and 20%-50% of patients with initially localised disease will develop metastases. The most common location of metastases is the liver, followed by the lung, peritoneum, and distant lymph nodes.

For patients with metastatic colorectal cancer (mCRC), first- and second-line treatments typically involve oxaliplatin or irinotecan combined with a fluoropyrimidine (5-fluorouracil or capecitabine), often in combination with targeted drug therapy such as vascular endothelial growth factor (VEGF) inhibitors (e.g. bevacizumab, aflibercept or ramucirumab) or epidermal growth factor receptor (EGFR) inhibitors (e.g. cetuximab or panitumumab) for patients with RAS wild-type. The multikinase inhibitors regorafenib and trifluridine/tipiracil (TAS-102) are approved standard third-line treatments for refractory mCRC.

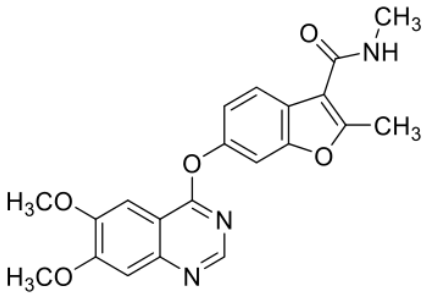
4 Quality aspects

4.1 Drug substance

INN: Fruquintinib

Chemical names:
IUPAC Name: 6-[(6,7-Dimethoxyquinazolin-4-yl)oxy]-N,2-dimethyl-1-benzofuran-3-carboxamide
CA Index Name: 3-Benzofurancarboxamide, 6-[(6,7-dimethoxy-4-quinazolinyl)oxy]-N,2-dimethyl-

Molecular formula: $C_{21}H_{19}N_3O_5$
Relative molecular mass: 393.39
Molecular structure:



Physicochemical properties: White to off-white non-hygroscopic powder. BCS class II.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is monitored with appropriate in-process controls and tests for isolated intermediates.

Specification: The structure of fruquintinib has been elucidated using spectroscopic techniques. To ensure a consistent quality, the specifications include the relevant test parameters as described in the current guidelines. Analytical methods are sufficiently described and validated according to ICH requirements. Batch data are within the specifications and consistent from batch to batch.

Stability: Appropriate stability data have been generated, resulting in suitable storage conditions and re-test period.

4.2 Drug product

Description and composition: Fruzaqla has been developed using standard excipients as immediate-release capsules in strengths of 1 mg and 5 mg.

Pharmaceutical development: Capsules were used throughout clinical development. Changes during development were minor (e.g. capsule colour, imprint).

Manufacture: The manufacturing process uses common pharmaceutical unit operations, such as weighing, mixing, and filling. Appropriate process controls have been established, and the process has been validated.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life are established. The analytical procedures are sufficiently described, and non-compendial methods are validated according to the current ICH requirements. Batch data are within the specifications and consistent from batch to batch.

Container closure system: HDPE bottles with desiccant are a standard pharmaceutical packaging configuration and have been demonstrated with stability studies to be appropriate for the product.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines, resulting in suitable storage conditions and shelf-life.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

6 Clinical aspects

Fruquintinib is a selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3.

The application for fruquintinib was part of an Access work-sharing procedure.

The PK of fruquintinib was well characterised in healthy subjects and the intended patient population. For details concerning clinical pharmacology see the attached Information for healthcare professionals.
No restriction on use in patients with renal impairment is required. Mild and moderate hepatic impairment had a limited effect on fruquintinib exposure but PK data are lacking in subjects with severe hepatic impairment. Fruquintinib can be used without restrictions in patients with mild hepatic impairment, but a lack of safety data in patients with moderate and severe hepatic impairment precludes use in these subgroups. In the pivotal FRESCO-2 study only patients with a serum total bilirubin ≤1.5 × ULN, ALT or AST ≤2.5 × ULN (without hepatic metastases) / ≤ 5 × ULN (with hepatic metastases) were included. Therefore, insufficient numbers of patients were studied for valid evaluation of safety in patients with moderate and severe hepatic impairment. Furthermore, treatment with fruquintinib is associated with grade 3-4, serious and grade 5 hepatic adverse events. Taking into account the clinical concerns and lack of data, fruquintinib is not recommended for use in patients with severe hepatic impairment. For details, please refer to the attached Information for healthcare professionals.

Fruquintinib has a low potential for interaction effects on other drugs, but is subject to clinically relevant effects of CYP3A inducers, which limits concomitant use.
The enzymes involved in one major metabolic elimination pathway of fruquintinib (M205 pathway) have not been identified. Thus, the interaction potential with regard to this pathway remains uncharacterised. As inhibition of the second major elimination pathway (via CYP3A4/5) as well as impaired hepatic function had only a limited effect on fruquintinib exposure, the risk of a strong, clinically relevant interaction via the M205 pathway is considered to be low. No specific recommendation can be given in the interaction section of the Information for healthcare professionals but the remaining risk is covered by the recommendation to modify the dose should adverse events (AEs) occur. For details concerning drug interactions see the attached Information for healthcare professionals.

The exposure-response (ER) analyses for safety supported the proposed recommendation for dose reductions in case of dermatological toxicity, haemorrhage, abnormal hepatic function, and proteinuria. In addition, the significantly increased risk of grade 3+ proteinuria and any grade haemorrhage under a continuous daily (QD) regimen support the selection of the fruquintinib regimen comprising once daily for 3 weeks followed by 1 week off (QD 3/1 regimen).

The applicant submitted results of 2 pivotal studies, FRESCO and FRESCO-2. However, FRESCO was evaluated only in Chinese patients who are not representative of the Swiss population. Therefore, results of the FRESCO study were regarded as supportive only.
The requested dose and recommended phase 2 dose (RP2D) for the pivotal studies FRESCO/FRESCO-2 of 5 mg once daily was evaluated in several phase 1 studies in Chinese patients with additional results from phase 1 US studies. For more details regarding dosing please refer to the attached Information for healthcare professionals.

Pivotal clinical trial FRESCO-2
FRESCO-2 is a global, randomised (2:1), double-blind, placebo-controlled, multicentre, Phase 3 study to compare the efficacy and safety of fruquintinib monotherapy in combination with best supportive care (BSC) vs placebo in combination with BSC in patients with mCRC.

Included patients had to have a histologically or cytologically documented metastatic colorectal adenocarcinoma and to have received all standard treatments, including fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if RAS wild-type), and had disease progression on or had been intolerant to trifluridine/tipiracil or regorafenib. Patients with deficient mismatch repair or microsatellite instability high tumours also had to have received an immune-checkpoint inhibitor and those with BRAFV600E-mutant tumours also had to have received a BRAF inhibitor, if approved and available. This is also reflected in the baseline characteristics with a median number of 5 prior treatment lines (> 3 lines: 83.3%).

Patients received 5 mg fruquintinib once daily plus best supportive care (BSC) or placebo once daily plus BSC for 21 days followed by a 7day break from therapy.

The primary endpoint of the study was overall survival (OS) and relevant secondary endpoints were progression-free survival (PFS) and overall response rate (ORR).

Overall, 691 patients were randomised (2:1; fruquintinib n=461 and placebo n=230). The median age was 64 years with 47% of patients ≥65 years. For more details regarding demographics please refer to the attached Information for healthcare professionals.

Overall, 92% of the patients received TAS-102 only or TAS-102 and regorafenib, 48% received regorafenib only or regorafenib and TAS-102, and 39% received both TAS-102 and regorafenib. Overall, 96.4% of patients had had prior treatment with VEGF inhibitors. Taking into account the mode of action of fruquintinib (inhibitor of VEGFR-1, 2, and 3), there might be a potential overlap with other antiangiogenic VEGF-targeting drugs. However, bevacizumab resistance is well known and targeting all 3 known VEGF receptors with fruquintinib, which is mechanistically distinct from an anti-VEGF therapy, may be suitable for patients in whom anti-VEGF therapy has failed.

The study met its primary endpoint of OS, with a statistically significant improvement among patients in the fruquintinib arm compared with the placebo arm (hazard ratio (HR) 0.66; 95% CI 0.55-0.80; stratified log-rank test p<0.001) with a median OS of 7.4 months vs 4.8 months (+2.6 months). According to the ESMO-Magnitude of clinical benefit scale (Form 2a) these results are scored as grade 3 (moderate clinical benefit). However, in this highly pretreated population with no other treatment options available, this benefit can be regarded as clinically meaningful.

The results of the FRESCO-2 study support the clinical relevance of angiogenesis inhibition. The results for PFS and OS with fruquintinib compared with placebo suggest that inhibition of the VEGF pathway remains an effective management strategy for mCRC, even in the later line setting and in patients with previous exposure to antiangiogenic agents.

The most common treatment emergent adverse events (TEAEs) in patients treated with fruquintinib were (≥20%) hypertension, asthenia, decreased appetite, diarrhoea, and hypothyroidism. In the fruquintinib arm compared with the placebo arm, a higher percentage of patients had grade 3 or 4 TEAEs (52.1% vs 30.9%). The rate of serious adverse events (SAEs) was comparable between treatment arms.

The most frequently reported adverse events of special interest of any grade in patients in the fruquintinib arm (≥20%) were hypertension, dermatological toxicity, thyroid dysfunction, abnormal hepatic function, and infections.

An increased risk of fatal or drug-induced liver injury meeting the Hy's law criteria was not observed in FRESCO-2. However, there is an increase in the risk of hepatic toxicity which can be mitigated through restriction of use and a warning including adequate monitoring. For details, please refer to the attached Information for healthcare professionals.

Supportive clinical trial FRESCO

The applicant submitted results of a second controlled study, FRESCO. The FRESCO study enrolled only Chinese patients in a different population than FRESCO-2. When the FRESCO study was conducted in China, the standard of care for the treatment of mCRC differed from the current standard of care in Western countries. In particular, neither third-line treatment with TAS-102 nor regorafenib was available in China at that time and none of the included patients in FRESCO had previously received TAS-102 or regorafenib. This was reflected in the demographics of FRESCO, where only approximately 30% of patients received prior bevacizumab. No patients received prior regorafenib since prior treatment with VEGFR tyrosine kinase inhibitors (TKIs) was not permitted. Therefore, this patient population was less exposed to previous treatments compared to the FRESCO-2 study, receiving less anti-VEGF biologic therapy with first- and second-line chemotherapy than in Western treatment paradigms. Taken together, the included study population was less pre-treated and not a representative patient population for Switzerland. Therefore, FRESCO is acceptable as a supportive study only.

An extrapolation from the results of the Asian population to the Swiss population is not justified. The safety comparison in the mCRC population presented differences that suggest that fruquintinib potentially has a different safety profile in Asian and non-Asian patients. Furthermore, in the published literature it is described that Asians and/or Pacific Islanders (API) as a whole experience a lower CRC incidence and better survival than other races/ethnic groups (Primm KM et al., Cancer Med., 2023).

Conclusion

In FRESCO-2 a statistically significant improvement in OS was reached among patients in the fruquintinib arm compared with the placebo arm. An OS benefit of +2.6 months in a heavily pretreated population with no other treatment options can be regarded as clinically meaningful.

The toxicity is manageable by experienced oncologists. Relevant safety aspects are adequately described in the Information for healthcare professionals.

The benefit-risk assessment is positive for fruquintinib in colorectal cancer after therapy progression on TAS-102 and/or regorafenib.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Fruzaqla was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

FRUZAQLA

Composition

Active substances

Fruquintinib.

Excipients

Capsule content: maize starch, cellulose, microcrystalline (E460), talc (E553b).

Capsule shell (1 mg hard capsules): gelatin, titanium dioxide (E171), tartrazine (E102) (0.0247 mg), sunset yellow FCF (E110) (0.0004 mg).

Capsule shell (5 mg hard capsules): gelatin, titanium dioxide (E171), allura red AC (E129) (0.1829 mg), brilliant blue FCF (E133).

Printing ink: dewaxed shellac (E904), propylene glycol (E1520), potassium hydroxide, iron oxide black (E172).

Pharmaceutical form and active substance quantity per unit

Hard capsules.

FRUZAQLA 1 mg hard capsules

Each hard capsule contains 1 mg fruquintinib. Opaque hard gelatin capsule, size 3 (approximate length 16 mm), with a yellow cap and a white body imprinted with “HM013” over “1mg” in black ink.

FRUZAQLA 5 mg hard capsules

Each hard capsule contains 5 mg fruquintinib. Opaque hard gelatin capsule, size 1 (approximate length 19 mm), with a red cap and a white body imprinted with “HM013” over “5mg” in black ink.

Indications/Uses

FRUZAQLA is used as monotherapy 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 chemotherapy, an anti-VEGF agent, and in the presence of wild-type RAS, with an anti-EGFR agent, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib (see “Properties/Effects”).

Dosage/Administration

FRUZAQLA should be initiated by a physician experienced in the administration of anticancer therapy.

Usual dosage

The recommended dose of fruquintinib is 5 mg (one 5 mg hard capsule) once daily at approximately the same time each day for 21 consecutive days, followed by a 7-day rest period to comprise a complete cycle of 28 days.

Duration of treatment

Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs.

Missed doses or vomiting

If a dose is missed by less than 12 hours, it should be taken, and the next dose should be taken as scheduled.

If a dose is missed by more than 12 hours, it should be skipped, and the next dose should be taken as scheduled.

The patient should not take two doses on the same day to make up for a missed dose.

If a patient vomits after taking a dose, the patient should not repeat the dose on the same day but resume the usual dosing as prescribed on the following day.

Dose adjustments following undesirable effects

The dose should be modified based on safety and tolerability. Fruquintinib should be permanently discontinued in patients unable to tolerate a dose of 3 mg once daily. The recommended dose reduction schedule for adverse reactions is provided in Table 1.

Table 1: Recommended FRUZAQLA dose reduction schedule

Dose reduction schedule	Dose and schedule	Number and strength of hard capsules
First dose reduction	4 mg once daily	Four 1 mg hard capsules / once daily
Second dose reduction	3 mg once daily	Three 1 mg hard capsules / once daily

The recommended dose modifications for adverse reactions are provided in Table 2.

Table 2: Recommended dose modification for FRUZAQLA for adverse reactions

Adverse reaction	Severity[1]	Dose modification
Hypertension	Grade 3	• Withhold if Grade 3 hypertension persists despite initiation or modification of antihypertensive treatment. • If hypertension recovers to Grade 1 or baseline, resume at the next lower dose as per Table 1. If the patient still experiences Grade 3 hypertension after taking 3 mg daily, permanently discontinue.
	Grade 4	Permanently discontinue.
Haemorrhagic events	Grade 2	• Withhold until bleeding fully resolves or recovers to Grade 1. • Resume at the next lower dose as per Table 1. If the patient still experiences Grade 2 haemorrhagic events after taking 3 mg daily, permanently discontinue.
	Grade ≥3	Permanently discontinue.
Proteinuria	≥2 g / 24 hours	• Withhold until proteinuria is <1 g / 24 hours or fully resolves • Resume at the next lower dose as per Table 1. If the patient still experiences ≥2 g / 24 hours proteinuria after taking 3 mg daily, permanently discontinue. Permanently discontinue for nephrotic syndrome.
Hepatotoxicity	Alanine-aminotransferase (ALT) or aspartate-aminotransferase (AST) greater than 3 times upper limit of normal (ULN) and total bilirubin ≤ 2 times ULN	• Withhold until AST, ALT and total bilirubin recover to Grade 1 or baseline. • Resume at the next lower dose as per Table 1. If the patient still experiences Grade 2 or Grade 3 liver function test abnormalities after taking 3 mg daily, permanently discontinue.

	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue.
	AST or ALT greater than 20 times ULN or bilirubin greater than 10 times ULN	Permanently discontinue.
Palmar-plantar erythrodysesthesia syndrome (PPES)	Grade 2	• Withhold and administer supportive treatment. • Resume at the same dose level if PPES has resolved completely or to Grade 1.
	Grade 3	• Withhold and administer supportive treatment. • Resume at the next lower dose as per Table 1 if PPES has resolved completely or to Grade 1. If the patient still experiences Grade 3 PPES after taking 3 mg daily, permanently discontinue.
Other adverse reactions	Grade 3	• Withhold. • Resume at the next lower dose as per Table 1 if reaction has resolved completely or to Grade 1. If the patient still experiences Grade 3 other adverse reactions after taking 3 mg daily, permanently discontinue.
	Grade 4	Discontinue. Consider resuming at the next lower dose as per Table 1 if the toxicity recovers to Grade 1 or baseline and the potential benefit outweighs the risks.

[1]Graded per national cancer institute common terminology criteria for adverse events. Version 5.0 (NCI CTCAE v5).

Special dosage instructions

Patients with renal disorders

No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see “Pharmacokinetics”).

Patients with hepatic disorders

No dose adjustment is required for patients with mild hepatic impairment (total bilirubin less than or equal to the ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) (see “Pharmacokinetics”).

FRUZAQLA has not been sufficiently studied in patients with moderate hepatic impairment (total bilirubin greater than 1.5 times and less than 3 times ULN and any AST).

FRUZAQLA is not recommended for use in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) as FRUZAQLA has not been studied in this population.

Elderly patients

No dose adjustment is required in patients aged 65 years or above.

Children and adolescents

FRUZAQLA is not authorised for use in the paediatric population.

Mode of administration

FRUZAQLA is for oral use. FRUZAQLA can be taken with or without food and should be swallowed as a whole hard capsule.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under “Composition”.

Warnings and precautions

Hypertension

Hypertension, including hypertensive crisis, has been reported in patients treated with fruquintinib. (see “Undesirable effects”). Pre-existing hypertension should be adequately controlled before starting fruquintinib treatment.

Hypertension should be medically managed with antihypertensive medicinal products and adjustment of the fruquintinib dose, if necessary (see “Dosage/Administration”). Fruquintinib should be permanently discontinued for hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis.

Haemorrhagic events

Haemorrhagic events have been reported in patients treated with fruquintinib, including gastrointestinal (GI) tract events (see “Undesirable effects”). Serious and sometimes fatal bleeding events have been reported in patients after treatment with fruquintinib.

Monitor haematologic and coagulation profiles more frequently in patients at risk for bleeding, including those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding requiring immediate medical intervention, fruquintinib should be permanently discontinued (see “Dosage/Administration”).

Infections

Infections have been reported in patients treated with fruquintinib, including fatal events (1%) in clinical studies (see “Undesirable effects”).

Fruquintinib should be withheld for Grade 3 or 4 infections or worsening of the infection of any grade. Fruquintinib to be resumed at the same dose when infection is resolved.

Gastrointestinal (GI) perforation

GI perforation events, including fatal events, have been reported in patients treated with fruquintinib (see “Undesirable effects”).

Symptoms of GI perforation should be periodically monitored during treatment with fruquintinib.

Fruquintinib should be permanently discontinued in patients developing GI perforation.

Hepatotoxicity

AST and ALT elevations have been reported in patients treated with fruquintinib, including ≥ Grade 3 undesirable events and fatal events (see “Undesirable effects”).

Liver function values (AST, ALT and bilirubin) should be monitored before initiation and throughout the treatment with fruquintinib. Based on the severity and persistence of liver function abnormalities, treatment should be withheld, and then reduced or permanently discontinued (see “Dosage/Administration”).

Proteinuria

Proteinuria events have occurred in patients treated with fruquintinib.

Urine protein should be monitored regularly. If urine dipstick proteinuria ≥ 2 g / 24 hours is detected, dose interruptions, adjustments, or discontinuation may be necessary. Fruquintinib should be permanently discontinued in patients developing nephrotic syndrome (see “Dosage/Administration”).

Palmar-plantar erythrodysaesthesia syndrome (PPES)

PPES is the most frequently reported dermatological adverse reaction (see “Undesirable effects”).

If Grade ≥ 2 skin reactions are detected, dose interruptions, adjustments, or discontinuation may be necessary (see “Dosage/Administration”).

Posterior reversible encephalopathy syndrome (PRES)

PRES has been reported with the use of fruquintinib (0.1%) (see “Undesirable effects”). PRES is a rare neurologic disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, discontinuation of fruquintinib, along with control of hypertension and supportive medical management of other symptoms, are recommended.

Impaired wound healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signalling pathway. No formal studies of the effect of fruquintinib on wound healing have been conducted.

Impaired wound healing has been reported in 1 patient (0.1%) treated with fruquintinib.

Patients are recommended to withhold fruquintinib for at least 2 weeks prior to surgery. Fruquintinib should not be resumed for at least 2 weeks after surgery as clinically indicated when there is evidence of adequate wound healing and there is a clinical need.

Arterial thromboembolic events

Fruquintinib may increase the risk of arterial thromboembolic events. Fruquintinib studies excluded patients with clinically significant cardiovascular diseases, uncontrolled hypertension, or with thromboembolic events within the past 6 months. Arterial thromboembolic events have been observed during treatment with fruquintinib.

It is recommended to avoid starting treatment with fruquintinib in patients with a history of thromboembolic events (including deep vein thrombosis and pulmonary embolism) within the past 6 months or if they have a history of stroke and/or transient ischemic attack within the last 12 months. If arterial thrombosis is suspected, fruquintinib should be discontinued immediately.

Aneurysms and arterial dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before starting treatment with fruquintinib, this risk should be carefully considered in patients with a history of risk factors such as hypertension or aneurysm.

Excipients

The 1 mg hard capsule contains tartrazine (E102), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of tartrazine (E102) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

The 1 mg hard capsule contains sunset yellow FCF (E110), which may cause allergic reactions.

The 5 mg hard capsule contains allura red (E129), which may cause allergic reactions.

Interactions

In vitro results indicated that fruquintinib was metabolised by CYP and non-CYP enzymes. CYP3A4 was the main enzyme among the CYP isoforms involved in the metabolism of fruquintinib, with minor contributions from CYP2C8, CYP2C9 and CYP2C19. Fruquintinib inhibited P-gp and BCRP in a dose-dependent manner *in vitro* and demonstrated pH-dependent aqueous solubility.

Effects of other medicinal products on the pharmacokinetics of fruquintinib

CYP3A inducers

The concomitant use of fruquintinib with strong and moderate CYP3A inducers should be avoided. No dose adjustment is required for fruquintinib with concomitant use of weak CYP3A inducers. Co-administration of fruquintinib with rifampicin (a strong CYP3A inducer) 600 mg once daily decreased fruquintinib area under the concentration time curve (AUC) by 65% and decreased fruquintinib C_{max} by 12%, and the geometric mean ratios (GMRs) with the associated 90% confidence intervals (CIs) of AUC_{inf} and C_{max} of fruquintinib in the presence of rifampicin versus fruquintinib alone were 0.35 (0.31; 0.39) and 0.88 (0.82; 0.94), respectively. Co-administration of fruquintinib with efavirenz (a moderate CYP3A inducer) 600 mg once daily is predicted to decrease fruquintinib AUC by 32% and fruquintinib C_{max} by 4%. No clinically meaningful differences in the AUC of fruquintinib are predicted when fruquintinib is coadministered with dexamethasone (a weak CYP3A inducer) 8 mg twice daily.

CYP3A inhibitors

No dose adjustment is required for fruquintinib with concomitant use of strong CYP3A inhibitors. Co-administration of fruquintinib with itraconazole (a strong CYP3A inhibitor) 200 mg twice daily did not result in clinically meaningful changes in the AUC and C_{max} of fruquintinib. The geometric mean ratios (GMRs) and the associated 90% confidence intervals (CIs) of AUC_{inf} and C_{max} of fruquintinib in the presence of itraconazole versus fruquintinib alone were 1.10 (1.04, 1.16) and 0.94 (0.86, 1.03), respectively.

Gastric acid reducing agents

No dose adjustment is required for fruquintinib with concomitant use of gastric acid lowering agents. Co-administration of fruquintinib with rabeprazole (a proton pump inhibitor) 40 mg once daily did not result in clinically meaningful changes in the AUC of fruquintinib. The GMRs and the associated 90% CIs of AUC_{inf} and C_{max} of fruquintinib in the presence of rabeprazole versus fruquintinib alone were 1.08 (1.01, 1.15) and 1.03 (0.94, 1.14), respectively.

Effect of fruquintinib on the pharmacokinetics of other medicinal products

Medicinal products that are substrates of P-glycoprotein (P-gp)

No dose adjustment is recommended for P-gp substrates during concomitant use with fruquintinib. Co-administration of a single dose of dabigatran etexilate 150 mg (a P-gp substrate) with a single dose of fruquintinib 5 mg decreased AUC of dabigatran by 9%, and the GMR with the associated 90% CI of the AUC_{inf} of dabigatran in the presence of fruquintinib versus dabigatran etexilate alone was 0.91 (0.68; 1.23).

Medicinal products that are substrates of breast cancer resistance protein (BCRP)

Caution is recommended when fruquintinib is used concomitantly with sensitive BCRP substrates. Co-administration of a single 10 mg dose of rosuvastatin (a BCRP substrate) with a single 5 mg dose of fruquintinib decreased AUC of rosuvastatin by 19%, and the GMR with the associated 90% CI of the AUC_{inf} of rosuvastatin in the presence of fruquintinib versus rosuvastatin alone was 0.81 (0.65; 1.02). However, with co-administration of a single 20 mg dose of rosuvastatin with multiple doses of fruquintinib, a mild increase in the AUC of rosuvastatin (a BCRP substrate) is not excluded.

In vitro studies

Cytochrome P450 enzymes: Fruquintinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A, or an inducer of CYP1A2, CYP2B6, CYP3A.

Transporter systems: Fruquintinib is not a substrate of P glycoprotein (P gp), organic anion transport protein (OATP)1B1, or OATP1B3. Fruquintinib is not an inhibitor of OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion protein (MATE)1, or MATE2-K.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential and men with female partners of childbearing potential should be advised to use effective contraception during and for at least 2 weeks following the last dose of fruquintinib.

Pregnancy

There are no clinical data available on the use of fruquintinib in pregnant women.

Based on its mechanism of action, fruquintinib has the potential to cause foetal harm. Studies in animals have shown reproductive toxicity, including foetal malformations (see “Preclinical data”).

FRUZAQLA should not be used during pregnancy unless the woman’s clinical condition requires treatment with fruquintinib and after careful consideration of the benefits for the mother and the risk to the foetus.

If fruquintinib is used during pregnancy or if the patient becomes pregnant while on treatment, the patient must be informed of the potential hazard to the foetus.

Lactation

It is unknown whether FRUZAQLA or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with FRUZAQLA and for at least 2 weeks after the last dose.

Fertility

There are no data on the effects of fruquintinib on human fertility. Results from animal studies indicate that fruquintinib may impair male and female fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Studies to evaluate the effects of fruquintinib on the ability to drive or operate machinery have not been conducted. Fruquintinib has a minor influence on the ability to drive and use machines. Fatigue may occur following administration of fruquintinib (see “Undesirable effects”).

Undesirable effects

Summary of the safety profile

The overall safety profile of fruquintinib is based on data from patients with mCRC who received at least one dose of (5 mg once daily 3 weeks on/1 week off each 28-day cycle) fruquintinib (n = 911) in clinical studies. In this patient population, the most common adverse reactions of any grade (incidence ≥ 20%) were hypertension (49.3%), anorexia (35.6%), proteinuria (35.5%), PPES (34.6%), hypothyroidism (32.4%), dysphonia (28.6%), diarrhoea (26.3%), and asthenia (24.5%), the majority of which were of Grades 1 or 2 in severity. The most common (incidence ≥ 5%) Grade 3/4 adverse reactions were hypertension (19.1%) and PPES (8.3%). The most common (incidence ≥ 1%) and important serious adverse reactions were gastrointestinal haemorrhage (1.5%), pneumonia (1.5%), hypertension (1.5%), and gastrointestinal perforation (1.3%) (see “Warnings and precautions”).

The frequency of treatment discontinuation due to adverse reactions was 7.6%. The most common adverse reaction leading to treatment discontinuation was proteinuria (1.6%).

The frequency of dose reduction due to adverse reactions was 20.5%. The most common adverse reactions leading to dose reduction were PPES (6.4%), hypertension (3.7%), and proteinuria (3.4%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies of fruquintinib are listed in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); not known (frequency cannot be estimated from the available data).

Table 3: Adverse reactions reported in clinical studies in patients with mCRC treated with fruquintinib (N=911)

System organ class	Frequency category	Adverse reactions All grades
Infections and infestations	Common	Pneumonia Upper respiratory tract infection[1]
Blood and lymphatic system disorders	Very Common	Thrombocytopenia[2] (15.6%)
	Common	Leukopenia[3] Neutropenia[4]
Endocrine disorders	Very Common	Hypothyroidism[5] (32.4%)
Metabolism and nutrition disorders	Very Common	Anorexia[6] (35.6%)
	Common	Hypokalaemia
Nervous system disorders	Uncommon	Posterior reversible encephalopathy syndrome
Vascular disorders	Very Common	Hypertension[7] (49.3%)
	Frequency not known	Aortic dissection*
Respiratory, thoracic and mediastinal disorders	Very Common	Dysphonia[8] (28.6%)
	Common	Epistaxis Throat pain[9]
Gastrointestinal disorders	Very Common	Diarrhoea (26.3%) Stomatitis[10] (19.8%)
	Common	Gastrointestinal haemorrhage[11] Pancreatic enzymes increased[12] Gastrointestinal perforation[13] Oral pain[14]
	Uncommon	Pancreatitis[15]

Hepatobiliary disorders	Very Common	Aspartate aminotransferase increased (18.9%) Total bilirubin increased[16] (17.9%) Alanine aminotransferase increased (16.4%)
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia syndrome (34.6%)
	Common	Rash[17]
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal discomfort[18] (13.7%) Arthralgia (13.5%)
Renal and urinary disorders	Very Common	Proteinuria[19] (35.5%)
General disorders and administration site conditions	Very Common	Asthenia (24.5%) Fatigue (19.8%)
	Common	Mucosal inflammation

The safety data based on the following pooled studies: 2012-013-00CH1; 2013-013-00CH1/FRESCO; 2019-013-GLOB1/FRESCO-2 including the open-label Japanese safety lead-in cohort; 2009-013-00CH1; 2012 013-00CH3; 2015-013-00US1. MedDRA 25.0.

* From the post-marketing phase

The following terms represent a group of related events that describe a medical condition rather than a single event:

[1]Includes nasopharyngitis, pharyngitis, upper respiratory tract infection

[2]Includes platelet count decreased and thrombocytopenia

[3]Includes leukopenia and white blood cell count decreased

[4]Includes neutropenia and neutrophil count decreased

[5]Includes blood thyroid stimulating hormone increased, hypothyroidism

[6]Includes appetite decreased and weight loss

[7]Includes blood pressure diastolic increased, blood pressure increased, diastolic hypertension, hypertension, hypertensive crisis

[8]Includes aphonia and dysphonia

[9]Includes laryngeal discomfort, laryngeal pain, oropharyngeal discomfort, oropharyngeal pain

[10]Includes aphthous ulcer, gingival ulceration, mouth ulceration, stomatitis, tongue ulceration

[11]Includes anal haemorrhage, anastomotic haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, intestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage

[12]Includes amylase increased, hyperamylasaemia, hyperlipasaemia, lipase increased

[13]Includes gastric perforation, gastric ulcer perforation, gastrointestinal perforation, intestinal perforation, large intestine perforation, rectal perforation, small intestinal perforation

[14]Includes gingival pain, oral pain, toothache

[15]Includes pancreatitis, pancreatitis acute

[16]Includes bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice, jaundice cholestatic

[17]Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic

[18]Includes bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain in extremity

[19]Includes albuminuria, protein urine present, proteinuria

Description of selected adverse reactions

Data for the following selected adverse reactions are based on patients (n=911) who received at least 1 dose of fruquintinib across three randomised placebo-controlled studies (2012-013-00CH1; 2013-013-00CH1/FRESCO; 2019-013-GLOB1/FRESCO-2). The management guidelines for these adverse reactions are described in sections “Dosage/Administration” and “Warnings and precautions”.

Hypertension

Hypertension was reported in 47.4% of patients treated with fruquintinib. Approximately half of these events occurred during the first 2 weeks after initiating treatment with fruquintinib. Grade ≥ 3 hypertension events were reported in 18.4% of patients. Two patients (0.3%) treated with fruquintinib experienced life-threatening hypertension. The majority of the events recovered or resolved following dose interruption or reduction, which occurred in 3.1% and 3.7% of patients, respectively. In 0.5% of patients, hypertension led to permanent treatment discontinuation.

Haemorrhagic events

Haemorrhagic events were reported in 26.5% of patients treated with fruquintinib. Most haemorrhagic events in patients treated with fruquintinib were mild to moderate in severity, the incidence of Grade ≥ 3 haemorrhagic events were 2.0%. Median time to onset in fruquintinib-treated patients was 23 days. Fatal haemorrhagic events were reported in 0.5% of patients. In 1.2% of patients treated with fruquintinib, haemorrhagic events led to dose discontinuation. The most common haemorrhagic reactions were gastrointestinal haemorrhage (7%) and epistaxis (5.6%). The most frequently reported serious haemorrhagic event was gastrointestinal haemorrhage in 1.5% of patients.

Infections

Infections were reported in 23.4% of patients treated with fruquintinib. Most infection events in patients treated with fruquintinib were mild to moderate in severity (incidence of Grade ≥ 3 infections

was 6%). Serious infections were reported in 4.1% of patients. Fatal infection events were reported in 1.0% of patients. The incidence of infections leading to dose discontinuation was 0.9%. The most common infections were upper respiratory tract infection (5.0%). The most frequently reported serious infection was pneumonia (1.4%).

Gastrointestinal (GI) perforation

Gastrointestinal perforation events were reported in 1.5% of patients treated with fruquintinib. Fatal GI perforation was reported in 0.1% of patients treated with fruquintinib. The most common GI perforation event was intestinal perforation (0.8%). The incidence of GI perforation events leading to dose discontinuation was 1.0%.

Proteinuria

Proteinuria was reported in 32.9% of the patients treated with fruquintinib. Most of the events were Grade 1 or Grade 2; the incidence of Grade ≥ 3 proteinuria events was 2.8%. Median time to onset in fruquintinib treated patients was 28 days. Most events recovered or resolved following dose interruption or reduction. In 1.8% of patients treated with fruquintinib, proteinuria led to permanent treatment discontinuation.

Palmar-plantar erythrodysaesthesia syndrome (PPES)

Palmar-plantar erythrodysaesthesia syndrome was reported in 32.7% of patients treated with fruquintinib. The incidence of Grade ≥ 3 PPES events was 8.5%. Median time to onset in fruquintinib-treated patients was 20 days. The majority of the events recovered (6.4%) or resolved (6.3%) following dose interruption or reduction. In 0.5% of patients treated with fruquintinib, PPES led to permanent treatment discontinuation.

Hypothyroidism

Hypothyroidism was reported in 31.5% of the patients treated with fruquintinib. Most of the events in patients treated with fruquintinib were Grade 1 or Grade 2; the incidence of Grade ≥ 3 hypothyroidism events was 0.3%. Median time to onset in fruquintinib-treated patients was 56 days. No events led to dose reduction or discontinuation.

Hepatotoxicity

Liver function test abnormalities (including AST, ALT, bilirubin) were reported in 36.4% of patients treated with fruquintinib. Most hepatobiliary disorders in patients treated with fruquintinib were mild to moderate in severity (incidence of Grade ≥ 3 liver function test abnormalities was 8.8%). The most common liver function test abnormality events were AST increase (18.1%), total bilirubin increase (18.3%), and ALT increase (15.5%). Median time to onset in fruquintinib treated patients was 28 days (range: 4 days to 12 months). Serious liver function test abnormalities were reported in 2.3% of patients. Fatal liver function test abnormalities were reported in 0.3% of patients. Liver function test

abnormalities led to dose interruption and reduction in 4.6% and 2.0% of patients, respectively, and to permanent discontinuation in 1.5% of patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

The highest dose of fruquintinib studied in clinical studies was 6 mg per day.

The effects of fruquintinib overdose are unknown, and there is no known antidote for fruquintinib overdose. In the event of an overdose, interrupt fruquintinib, general supportive measures should be undertaken and observe until clinical stabilisation.

Properties/Effects

ATC code

L01EK04

Mechanism of action

Fruquintinib is a selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3 (IC_{50} values of 33, 35, and 0.5 nM, respectively) with antitumour effects resulting from suppression of tumour angiogenesis and tumour deprivation of nutrients and oxygen.

Pharmacodynamics

See “Mechanism of action”.

Cardiac electrophysiology

No prolongation of heart rate-corrected QT (QTc) interval (> 20 milliseconds) was observed at the recommended dosage of fruquintinib.

Clinical efficacy

The efficacy and safety of fruquintinib plus best supportive care (BSC) were evaluated in one randomised, placebo-controlled, double-blind, phase III study (FRESCO-2) in patients with mCRC previously treated with but not limited to oxaliplatin or irinotecan-based chemotherapies. The clinical efficacy of fruquintinib in the FRESCO-2 study is described below.

FRESCO-2 study

The clinical safety and efficacy of fruquintinib was evaluated in a global, randomised, double-blind, placebo-controlled, multicentre, phase III study (FRESCO-2) in 691 patients with previously treated

mCRC. Patients were stratified according to prior therapy (trifluridine/tipiracil [52.2%] vs. regorafenib [8.4%] vs. both [39.4%]), RAS mutation status (wild-type [36.9%] vs. [63.1%] mutant) and duration of metastatic disease (≤ 18 months [7.2%] vs. > 18 months [92.8%]). The primary endpoint was OS. The key secondary endpoint was PFS. Other secondary endpoints included tumour objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and safety.

In total, 691 patients were randomised (2:1) to receive fruquintinib 5 mg orally once daily (N=461) plus BSC or placebo orally once daily (N=230) (hereafter referenced as fruquintinib and placebo respectively) plus BSC, for 21 days on therapy followed by 7 days off therapy in a 28-day treatment cycle.

Among the 691 randomised patients, the median age was 64 years (range: 25 to 86), with 47% ≥ 65 years of age. 55.7% of patients were male, 80.9% were White, and had an ECOG performance status of 0 (43.1%) or 1 (56.9%). Tumour RAS wild-type was reported in 36.9% of patients at study entry. The median number of prior lines of therapy for metastatic disease was 4 (range 2 to 16). 82.5% of the patients had more than three previous lines of therapy (72.6% for metastatic disease) and a total of 5 patients had two previous lines of therapy. Six out of the 9 patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours had prior immune checkpoint inhibitor therapy.

In addition to treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, 96.4% of patients had prior anti-VEGF therapy, 38.8% had prior anti-EGFR therapy. In addition, a total of 91.6% of the patients had progression to trifluridine/tipiracil or trifluridine/tipiracil and regorafenib, 52.2% of them after therapy with trifluridine/tipiracil, 8.4% after therapy with regorafenib, 39.4% after therapy with trifluridine/tipiracil and regorafenib. In addition, 4.6% received immunotherapy, and 2.3% received a BRAF inhibitor.

The addition of fruquintinib to BSC resulted in a statistically significant improvement in overall survival (OS) and progression-free survival (PFS) compared to placebo plus BSC. The hazard ratio for OS was 0.66 [95% CI 0.55, 0.80], with median OS of 7.4 months and 4.8 months, respectively ($p < 0.001$). The hazard ratio for PFS was 0.32 [95% CI 0.27, 0.39], with median PFS of 3.7 months and 1.8 months, respectively ($p < 0.001$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with FRUZAQLA in all subsets of the paediatric population in metastatic colorectal cancer (see “Dosage/Administration”).

Pharmacokinetics

Absorption

After oral administration of fruquintinib, the median time to achieve peak plasma fruquintinib concentration (T_{max}) was approximately 2 hours. Following repeat once-daily dosing, fruquintinib exposure (C_{max} and $AUC_{0\text{-}24h}$) increased in a dose-proportional manner across the dose range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage). Following administration of fruquintinib 5 mg once daily for 21 days with 7 days off of each 28-day cycle in patients with advanced solid tumours, steady state of fruquintinib was achieved after 14 days. Fruquintinib accumulates at steady-state: The mean $AUC_{0\text{-}24h}$ was 4-fold relative to a single dose. At the recommended dose of 5 mg of FRUZAQLA, the geometric mean (%CV) C_{max} and $AUC_{0\text{-}24h}$ for fruquintinib at steady-state were 300 ng/mL (28%) and 5880 ng*h/mL (29%), respectively.

Effect of food

Compared to a fasting intake, a high-fat meal had no clinically meaningful effect on fruquintinib pharmacokinetics in healthy subjects.

Distribution

The apparent volume of distribution of fruquintinib is approximately 48.5 L. Plasma protein binding of fruquintinib is approximately 95% *in vitro*.

Metabolism

Fruquintinib is metabolised by multiple enzymes, including CYP450 (CYP3A and CYP2C subfamilies) and non-CYP450 enzyme systems. The *in vivo* metabolism and mass balance study of [^{14}C] labelled fruquintinib showed that fruquintinib mainly exists in human plasma in its unchanged form, accounting for approximately 72% of total exposure in the plasma, and the CYP3A4-mediated *N*-demethyl metabolite of fruquintinib accounts for approximately 17% of total exposure in plasma. Other metabolic pathways include multi-site mono-oxidation, *O*-demethylation, *N*-demethylation, *O*-dequinazoline ring, and amide hydrolysis. The phase II metabolites are mainly glucuronic acid and sulphuric acid conjugates of phase I products.

Elimination

The apparent clearance (CL/F) of fruquintinib is 14.8 mL/min at steady state after once daily dosing in patients with advanced solid tumours. The mean elimination half-life of fruquintinib is approximately 42 hours.

Following administration of a single 5 mg dose of radiolabelled fruquintinib in healthy subjects, approximately 60% of the dose was recovered in urine (0.5% of the dose as unchanged fruquintinib), and 30% of the dose was recovered in faeces (5% of the dose as unchanged fruquintinib).

Kinetics in specific patient groups

Renal impairment

Based on the population pharmacokinetic analyses, mild to moderate renal impairment (CrCL 30 to 89 mL/min) had no clinically meaningful impact on fruquintinib pharmacokinetics. Based on a dedicated renal impairment pharmacokinetic study, following administration of a single 5 mg or 2 mg oral dose of FRUZAQLA in subjects with moderate (CrCL 30-59 mL/min, N=8) or severe renal impairment (CrCL 15-29 mL/min, N=8), respectively, no clinically meaningful differences in fruquintinib dose-normalised exposures were observed in subjects with moderate or severe renal impairment compared to subjects with normal renal function (CrCL ≥ 90 mL/min), N=8).

Hepatic impairment

No clinically meaningful differences in the pharmacokinetics of fruquintinib were observed between patients with normal hepatic function and patients with mild (total bilirubin ≤ ULN with AST greater than ULN or total bilirubin > 1 to 1.5 times ULN with any AST) hepatic impairment based on population pharmacokinetic analyses. Based on a dedicated hepatic impairment pharmacokinetic study, following administration of a single 2 mg oral dose of FRUZAQLA, no clinically meaningful differences in the dose-normalised AUC of fruquintinib were observed in subjects with moderate (Child-Pugh B, N=8) hepatic impairment compared to subjects with normal hepatic function (N=8).

Age, body weight, gender, race or ethnicity

Population pharmacokinetic analyses showed that age (18 to 82 years), body weight (48 to 108 kg), gender, race (Asian, Black, and White), or ethnicity (Hispanic/Latino vs. non-Hispanic/Latino) had no clinically relevant impact on the pharmacokinetics of fruquintinib.

Children and adolescents

No pharmacokinetic studies were performed with fruquintinib in patients under 18 years of age.

Preclinical data

In repeat-dose toxicity and reproductive toxicity studies, toxicity was observed at fruquintinib average plasma concentrations below the expected human therapeutic concentrations.

Repeat dose toxicity

In repeat-dose animal toxicity studies, the main toxicities were identified in the gastrointestinal tract, hepatobiliary system, immune system, skeletal system (femur and teeth), kidneys, hematopoietic system, and adrenal gland. All findings were reversible or at least partially reversible after 4 weeks without treatment, apart from the adrenal gland and the skeletal system (broken/lost teeth).

Genotoxicity

No evidence of genotoxicity was observed in *in vitro* and *in vivo* studies.

Carcinogenicity

Carcinogenicity studies have not been conducted with fruquintinib.

Impairment of fertility

In a fertility and early embryonic development study in rats, male and female reproductive indices were decreased at exposures approximately 3.2 and 0.8-fold the human AUC, respectively. Dose dependent increases in pre-implantation loss were observed in the same study.

Reproductive toxicity

In an embryo-foetal developmental study in rats, embryo-foetal toxicity as well as external, visceral, and skeletal malformations were observed.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date marked as “EXP” on the pack.

Special precautions for storage

Keep out of the reach of children.

Do not store above 30 °C.

Store in the original packaging in order to protect the contents from moisture.

Keep the bottle tightly closed.

Do not remove desiccant from the bottle.

Authorisation number

69524 (Swissmedic).

Packs

FRUZAQLA 1 mg: Bottle with 21 hard capsules (A).

FRUZAQLA 5 mg: Bottle with 21 hard capsules (A).

Marketing authorisation holder

Takeda Pharma AG, 8152 Opfikon, Switzerland.

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