▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

FRUZAQLA (FRUQUINTINIB)

1 NAME OF THE MEDICINE

fruquintinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FRUZAQLA 1 mg hard capsules
FRUZAQLA 1 mg hard capsules contain 1 mg fruquintinib. Excipients with known effect: Each 1 mg hard capsule contains tartrazine.

FRUZAQLA 5 mg hard capsules
FRUZAQLA 5 mg hard capsules contain 5 mg fruquintinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

FRUZAQLA 1 mg hard capsules
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
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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FRUZAQLA is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, and an anti-EGFR agent if appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Posology and method of administration
The recommended dose of FRUZAQLA is 5 mg taken orally once daily (at approximately the same time each day) for the first 21 days of each 28-day cycle. FRUZAQLA capsules should be swallowed whole, and can be taken with or without food.

Duration of treatment
Treatment with FRUZAQLA 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.

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 scheduled on the following day.

Dose adjustments for adverse reactions
The recommended dose reduction schedule for adverse reactions is provided in Table 1.

Table 1: Recommended FRUZAQLA dose reduction schedule

Dose reduction level	**Dose and schedule**
First dose reduction level	4 mg orally once daily for the first 21 days of each 28-day cycle
Second dose reduction level	3 mg orally once daily for the first 21 days of each 28-day cycle
Third dose reduction level	Permanently discontinue FRUZAQLA

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 despite optimal antihypertensive therapy	Withhold FRUZAQLA. If hypertension recovers to ≤Grade 1 or baseline, resume at a reduced dose (see Table 1).
	Grade 4 or life-threatening	Permanently discontinue FRUZAQLA.
Haemorrhage	Grade 2	Withhold FRUZAQLA. If bleeding recovers to ≤Grade 1, resume at a reduced dose (see Table 1).
	Grade ≥3	Permanently discontinue FRUZAQLA.
Proteinuria	≥2 g in 24 hours	Withhold FRUZAQLA. If proteinuria recovers to <1 g / 24 hours, resume at a reduced dose (see Table 1).
	≥2 g in 24 hours after a 3 mg dose; or nephrotic syndrome	Permanently discontinue FRUZAQLA.

Liver function test (LFT) abnormalities	ALT or AST >3 x ULN/baseline;[2] or total bilirubin >1.5 x ULN/baseline[2]	Withhold FRUZAQLA. If AST/ALT and total bilirubin resolve to ≤Grade 1 or baseline, resume at a reduced dose (see Table 1).
	ALT or AST >3 x ULN with concurrent total bilirubin >2 x ULN (in the absence of alternative aetiologies)	Permanently discontinue FRUZAQLA.
	AST or ALT >20 x ULN/baseline;[2] or bilirubin >10 x ULN/baseline[2]	Permanently discontinue FRUZAQLA.
Palmar-plantar erythrodysaesthesia syndrome (PPES)	Grade 2	Withhold FRUZAQLA and provide supportive treatment. If PPES recovers to ≤Grade 1, resume at the same dose level.
	Grade 3	Withhold FRUZAQLA and provide supportive treatment. If PPES recovers to ≤Grade 1, resume at a reduced dose level (see Table 1).
Other adverse reactions	Grade 3	Withhold FRUZAQLA. If toxicity recovers to ≤Grade 1 or baseline, resume at a reduced dose (see Table 1).
	Grade 4	Discontinue FRUZAQLA. If the toxicity is not life-threatening, recovers to ≤Grade 1 or baseline, and the potential benefit outweighs the risks, consider resuming at a reduced dose (see Table 1).

Alanine aminotransferase = ALT; aspartate aminotransferase = AST; ULN = upper limit of normal
[1] Grades refer to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5).
[2] ULN or baseline: whichever is higher.

Special populations

Renal impairment
No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (elevated AST and normal total bilirubin, or total bilirubin 1 to 1.5 x the upper limit of normal [ULN] with any AST; see section 5.2). Inadequate data are available to support dose recommendations for moderate hepatic

impairment (total bilirubin >1.5 to 3 x ULN and any AST). FRUZAQLA is not recommended for use in patients with severe hepatic impairment (total bilirubin >3 x ULN and any AST).

Elderly population
No dose adjustment is required for elderly patients.

Paediatric population
The safety and efficacy of FRUZAQLA in patients aged 0 to <18 years have not been established. No data are available.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypertension
FRUZAQLA can cause hypertension. Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, hypertension occurred in 49%, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). The median time to first onset of hypertension was 14 days from first dose of FRUZAQLA (see also section 4.8). Do not initiate FRUZAQLA unless blood pressure is adequately controlled. Monitor blood pressure weekly the first month, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on the severity of hypertension (see section 4.2).

Haemorrhage
FRUZAQLA can cause serious haemorrhagic events, which may be fatal. Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, 6% experienced a gastrointestinal haemorrhage, including 13 Grade ≥3 events (1% of patients) and 2 fatal events (0.2% of patients). See also section 4.8. Monitor haematologic and coagulation profiles more frequently in patients at risk for bleeding, including due to concomitant anticoagulants. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on the severity of haemorrhage (see section 4.2).

Infections
FRUZAQLA treatment may cause an increased risk of infections, including fatal infections. Amongst 911 patients with mCRC who received FRUZAQLA across these and other clinical trials, the most common infections were urinary tract infections (6.8%), upper respiratory tract infections (3.2%) and pneumonia (2.5%); fatal infections included pneumonia (0.4%), sepsis (0.2%), bacterial infection (0.1%), lower respiratory tract infection (0.1%), and septic shock (0.1%). The most common fatal infection was pneumonia (see also section 4.8). Withhold FRUZAQLA for Grade 3 or 4 infections, or worsening of an infection of any grade. Resume FRUZAQLA at the same dose when the infection is resolved.

Gastrointestinal (GI) perforation
Medicines that inhibit the vascular endothelial growth factor (VEGF) signalling pathway can cause GI perforation (see section 4.8). Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, twelve patients (1.3%) experienced a Grade ≥3 gastrointestinal perforation, including one fatal event (0.1%). Permanently discontinue FRUZAQLA if gastrointestinal perforation or fistula occurs.

Hepatotoxicity
FRUZAQLA can cause liver injury. Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, 48% experienced increased ALT or AST, including Grade ≥3 events in 5%, and fatal events in 0.2%. Median time to first onset of elevated liver enzymes was 29 days from first dose of FRUZAQLA (see also section 4.8). Monitor liver function tests (ALT, AST, and bilirubin) before initiation and periodically throughout treatment with FRUZAQLA. Withhold, reduce dose or permanently discontinue FRUZAQLA depending on the severity and persistence of hepatic enzyme derangement (see section 4.2).

Proteinuria
FRUZAQLA can cause proteinuria. Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, 36% experienced proteinuria and 2.5% of patients experienced Grade ≥3 events. Median time to first onset of proteinuria was 22 days from first dose of FRUZAQLA (see also section 4.8). Monitor for proteinuria before initiation and periodically throughout treatment with FRUZAQLA. Withhold, reduce dose or permanently discontinue FRUZAQLA depending on the severity and persistence of proteinuria, or presence of nephrotic syndrome (see section 4.2).

Palmar-plantar erythrodysaesthesia syndrome (PPES)
FRUZAQLA can cause PPES. Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, PPES occurred in 35%, including 8% with Grade 3 events. Median time to first onset of PPES was 19 days from first dose of FRUZAQLA (see also section 4.8). Depending on severity, withhold FRUZAQLA for PPES and resume at the same or a reduced dose (see section 4.2).

Posterior reversible encephalopathy syndrome (PRES)
FRUZAQLA can cause PRES, a syndrome of subcortical vasogenic oedema diagnosed by characteristic finding on MRI. PRES occurred in one of 911 patients (0.1%) with mCRC who received FRUZAQLA in clinical trials. Perform an evaluation for PRES in any patient presenting with seizures, headache, visual disturbances, altered consciousness or cognition, or other evidence of neurological dysfunction. Discontinue FRUZAQLA in patients who develop PRES.

Impaired wound healing
Impaired wound healing can occur in patients receiving medicines that inhibit the VEGF signalling pathway. Amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, 1 patient (0.1%) experienced a Grade 2 event of wound dehiscence. Do not administer FRUZAQLA for at least 2 weeks prior to surgery. Do not administer FRUZAQLA until adequate wound healing. The safety of resumption of FRUZAQLA after resolution of wound healing complications has not been established.

Arterial thromboembolic events
FRUZAQLA may increase the risk of arterial thromboembolic events. FRUZAQLA studies excluded patients with clinically significant cardiovascular disease, uncontrolled hypertension, or with thromboembolic events within the prior 6 months. Despite this, amongst 911 patients with mCRC who received FRUZAQLA in clinical trials, 7 patients (0.8%) experienced an arterial thromboembolic event. This risk should be carefully considered in deciding whether or not to initiate treatment with FRUZAQLA in a patient with a recent history of thromboembolic events. Discontinue FRUZAQLA if arterial thromboembolism occurs.

Use in the elderly
No overall differences in pharmacokinetics, safety or efficacy were observed between elderly (aged 65 years and above) and those younger than 65 years.

Paediatric use
The safety and efficacy of FRUZAQLA in patients younger than 18 years of age have not been established.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro studies
Cytochrome P450 enzymes:
Fruquintinib is metabolised by CYP and non-CYP enzymes *in vitro*. CYP3A4 was the main CYP enzyme isoform involved, with minor contributions from CYP2C8, CYP2C9 and CYP2C19. 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 at clinically relevant concentrations.

Effects of other medicinal products on the pharmacokinetics of FRUZAQLA

CYP3A inducers
Coadministration of fruquintinib with rifampicin (a strong CYP3A inducer) 600 mg once daily decreased fruquintinib AUC by 65% and decreased C_{max} by 12% . Coadministration 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. The concomitant use of FRUZAQLA with strong and moderate CYP3A inducers should be avoided.

CYP3A inhibitors
Co-administration of fruquintinib with itraconazole (a strong CYP3A inhibitor) 200 mg twice daily did not result in clinically meaningful changes to fruquintinib exposure.

Gastric acid lowering agents
Fruquintinib demonstrated pH-dependent aqueous solubility *in vitro*. However, co-administration of FRUZAQLA with rabeprazole (a proton pump inhibitor) 40 mg once daily did not result in clinically meaningful changes to fruquintinib exposure.

Effect of fruquintinib on the pharmacokinetics of other medicinal products
Medicinal products that are substrates of P-glycoprotein (P-gp)
Fruquintinib inhibited P-gp in a dose-dependent manner *in vitro*. Co-administration of a single dose of dabigatran etexilate 150 mg (a P-gp substrate) with a single dose of FRUZAQLA 5 mg decreased AUC of dabigatran by 9%. Co-administration of a single dose of digoxin (a P-gp substrate) 0.5 mg with multiple doses of FRUZAQLA is predicted to result in a 6% increase in AUC of digoxin. This effect is not likely to be clinically significant, and no dose adjustment is recommended for P-gp substrates during concomitant use with FRUZAQLA.

Medicinal products that are substrates of breast cancer resistance protein (BCRP)
Fruquintinib inhibited BCRP in a dose-dependent manner *in vitro*. Co-administration of a single 10 mg dose of rosuvastatin (a BCRP substrate) with a single 5 mg dose of FRUZAQLA decreased AUC of rosuvastatin by 19%. Co-administration of a single 20 mg dose of rosuvastatin with multiple doses of FRUZAQLA is predicted to result in a 19% increase in AUC of rosuvastatin (a BCRP substrate). This effect is not likely to be clinically significant, and no dose adjustment is recommended for BCRP substrates during concomitant use with fruquintinib.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effects of FRUZAQLA on human fertility. In a fertility and early embryonic development study *via* oral route in rats, no effect was seen on male and female fertility at 3 and 0.5 mg/kg/day, respectively (1.2 and 0.19 times the exposure at the maximum recommended human dose [MRHD] based on AUC, respectively).

Use in pregnancy – Pregnancy Category D
Based on findings in animal studies (see below) and its mechanism of action, FRUZAQLA has the potential to cause fetal harm if administered to a pregnant person. Advise all patients of the potential risk to a fetus. Advise patients who could become pregnant or whose partner could become pregnant to use effective contraception during treatment with FRUZAQLA and for at least 2 weeks after the last dose.

In an embryo-fetal development study in pregnant rats, following oral administration of fruquintinib during the period of organogenesis, embryotoxic and teratogenic effects were observed at exposures below the clinical exposure (doses ≥ 0.1 mg/kg/day; 0.05 times the clinical exposure at MRHD based on AUC). Observations included fetal external (head and tail malformations and oedema), visceral (malpositioned or absent blood vasculature), and skeletal (lumbar hemi-vertebrae) malformations. Other skeletal anomalies included unossified forelimb metacarpals and phalanx, misaligned or unossified caudal vertebrae, supernumerary lumbar vertebra, bipartite or unilateral ossification of the lumbar centrum, and bipartite, incomplete, unilateral or nonossification of the thoracic centrum at ≥ 0.1 mg/kg/day. In a fertility and early embryonic developmental study in rats, embryo resorption and post-implantation loss were increased, resulting in decreased viable fetuses, at 0.5 mg/kg/day (0.19 times the clinical exposure at MRHD based on AUC).

Use in 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Studies to evaluate the effects of FRUZAQLA on the ability to drive or operate machinery have not been conducted. Fatigue is very common amongst patients taking FRUZAQLA (see section 4.8).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The pooled safety population described in section 4.4 reflects exposure to FRUZAQLA as a single agent in 911 patients with mCRC who received at least one dose of FRUZAQLA at the recommended dosage across multiple studies: 781 patients from three randomised, placebo-controlled studies (FRESCO-2 [2019-013-GLOB1], FRESCO [2013-013-00CH1] and 2012-013-00CH1); 124 patients from three open-label studies (2009-013-00CH1, 2012-013-00CH3 and 2015-013-00US1); and 6 patients from an open-label lead-in cohort of FRESCO-2. Amongst the 911 patients who received FRUZAQLA, the median exposure was 3.7 months; 23% were exposed for 6 months or longer and 3.5% were exposed for greater than one year. The median age was 60 years (range: 23 to 82) and 34% were 65 years of age or older.

Tabulated list of adverse reactions

FRESCO-2 study

The safety of FRUZAQLA was evaluated in FRESCO-2, a randomised, double-blind, placebo-controlled study (see Section 5.1). Patients received either FRUZAQLA 5 mg daily for the first 21 days of each 28-day cycle plus best supportive care (BSC) (n=456) or matching placebo plus BSC (n=230).

The median duration of therapy with FRUZAQLA was 3 months (range: 0.3 to 19.1 months).

Serious adverse reactions occurred in 38% of patients treated with FRUZAQLA. Serious adverse reactions in ≥2% of patients treated with FRUZAQLA included haemorrhage (2.2%) and gastrointestinal perforation (2.0%). Fatal adverse reaction(s) occurred in 14 (3.1%) patients who received FRUZAQLA. Fatal adverse reactions occurring in ≥2 patients include pneumonia (n=3), sepsis/septic shock (n=2), and hepatic failure/encephalopathy (n=2).

Adverse reactions leading to treatment discontinuation occurred in 20% of patients treated with FRUZAQLA. Adverse reactions leading to treatment discontinuations of FRUZAQLA in ≥1% of patients were asthenia and gastrointestinal perforation.

Dose interruptions of FRUZAQLA due to an adverse reaction occurred in 47% of patients. Adverse reactions leading to dose interruptions of FRUZAQLA in ≥2% of patients were PPE, proteinuria, asthenia, abdominal pain, hypertension, vomiting, and diarrhoea.

Dose reductions of FRUZAQLA due to an adverse reaction occurred in 24% of patients. Adverse reactions leading to dose reductions of FRUZAQLA in ≥2% of patients were PPE, hypertension and asthenia.

Table 3 summarises the adverse reactions in FRESCO-2.

Table 3 Adverse reactions with a ≥10% incidence in patients who received FRUZAQLA, and with a ≥5% higher incidence than in the placebo arm in FRESCO-2.

Adverse reaction	FRUZAQLA (N=456)		Placebo (N=230)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General				
Fatigue[1]	53	12	39	4.8
Vascular				
Hypertension[1]	38	14	9	0.9
Gastrointestinal				
Stomatitis[1]	31	2.2	7.8	0.4
Abdominal pain[1]	25	3.5	20	3

Diarrhoea[1]	24	3.7	11	0
Endocrine disorders				
Hypothyroidism	21	0.4	0.4	0
Skin and subcutaneous				
PPES	19	6	2.6	0
Renal				
Proteinuria[1]	18	1.8	5	0.9
Respiratory				
Dysphonia[1]	18	0	5	0
Musculoskeletal				
Musculoskeletal pain[1]	16	1.1	7	0
Arthralgia	11	0.9	4.3	0

PPES = palmar-plantar erythrodysaesthesia syndrome (hand-foot skin reaction)

[1] Represents a composite of multiple related terms.

Other important adverse reactions (all grades) that occurred in <10% of patients treated with FRUZAQLA included urinary tract infection (4.6%), epistaxis (3.9%), proctalgia (3.5%), pneumonia (2.4%), gastrointestinal haemorrhage (1.5%), gastrointestinal perforation (1.3%), pancreatitis (0.7%), thrombotic microangiopathy (0.2%), and posterior reversible encephalopathy syndrome (0.2%).

Table 4 describes selected laboratory abnormalities observed in FRESCO-2.

Table 4 Selected laboratory abnormalities that worsened from baseline in ≥20% of patients receiving FRUZAQLA in FRESCO-2

Laboratory[1] abnormality	**FRUZAQLA (N=456)[2]**		**Placebo (N=230)[2]**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Chemistry				
Triglycerides increased	53	2.8	22	1.0
Cholesterol increased	37	1.9	22	1.9
AST increased	36	4.3	24	1.9
Albumin decreased	35	1.6	32	1.4
Sodium decreased	35	1.1	27	0.9
ALT increased	34	5	22	1.4
Bilirubin increased	30	7	21	8
ALP increased	20	1.6	27	0.5
Magnesium decreased	20	0.5	10	0.5
Haematology				
Lymphocytes decreased	30	6	32	4.7
Platelets decreased	30	0.2	4.7	0
APTT increased	21	2.7	18	1.5

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; N = number of patients

[1] Graded according to NCI CTCAE version 5.0.

[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FRUZAQLA (range: 409-444) and placebo (range: 195-216).

Other important laboratory abnormalities (all grades) that occurred in <20% of patients treated with FRUZAQLA included pancreatic enzymes increased (3.9%).

FRESCO study

The safety of FRUZAQLA was generally similar in a Chinese population who had not previously received regorafenib or trifluridine/tipiracil who took part in an earlier, randomised, double-blind, placebo-controlled study, FRESCO (see section 5.1). The median duration of therapy with FRUZAQLA in FRESCO was 3.68 months (range: 0.3 to 22.1 months).

Serious adverse reactions occurred in 15% of patients treated with FRUZAQLA. Serious adverse reactions in ≥2% of patients included intestinal obstruction (2.9%) and haemorrhage (2.2%). Fatal adverse reaction(s) occurred in 7 (2.5%) patients who received FRUZAQLA including cerebral infarction (n=1), gastrointestinal haemorrhage (n=1), haemoptysis (n=1), bacterial infection (n=1), lung/lower respiratory infection (n=2), and multiple organ dysfunction (n=1).

Adverse reactions leading to treatment discontinuation occurred in 15% of patients who received FRUZAQLA. Adverse reactions leading to treatment discontinuations of FRUZAQLA in ≥1% were intestinal obstruction, proteinuria and hepatic function abnormalities.

Dose interruptions of FRUZAQLA due to an adverse reaction occurred in 35% of patients. Adverse reactions leading to dose interruptions of FRUZAQLA in ≥2% of patients were PPE, proteinuria, platelet count decreased, ALT increased, hypertension, and diarrhoea.

Dose reductions of FRUZAQLA due to an adverse reaction occurred in 24% of patients. Adverse reactions leading to dose reduction of FRUZAQLA in ≥2% of patients were PPE, proteinuria, and hypertension.

In FRESCO, proteinuria was very common in both the FRUZAQLA arm (55%, including 4.7% incidence of grade 3-4 events) and the placebo arm (30%, with no grade 3 or 4 events). Haemorrhages were reported in 28% of the FRUZAQLA arm (including Grade 3-4 events in 1%) and 14% of the placebo arm in FRESCO. PPES was also very common in FRESCO, occurring in 49% of patients who received FRUZAQLA, including 11% who experienced grade 3-4 PPES, whilst there was an incidence of 2.9% (with no grade 3-4 events) in the placebo arm. Common reactions were otherwise similar in FRESCO to FRESCO-2.

Other clinically important adverse reactions (all grades) that occurred in <10% of patients treated with FRUZAQLA in FRESCO included urinary tract infection (9%), rash (9%), upper respiratory tract infection (4.7%), proctalgia (3.6%), pneumonia (2.9%), and gastrointestinal perforation or fistula (2.2%).

Laboratory abnormalities were similar in FRESCO to FRESCO-2. Creatinine increase from baseline occurred in 87% (0.7% Grade 3-4) of the FRUZAQLA arm and 75% (1.5% Grade 3-4) of the placebo arm. Calcium decrease occurred in 25% (0.4% Grade 3-4) of the FRUZAQLA arm and 13% (0% Grade 3-4) of the placebo arm. decrease was notably more common with FRUZAQLA than placebo, similarly to in FRESCO-2.

Other important laboratory abnormalities (all grades) that occurred in <20% of patients treated with FRUZAQLA included pancreatic enzymes increased (4.3%).

Description of selected adverse reactions

Data for the following selected adverse reactions are based on patients who received at least 1 dose (5 mg) of fruquintinib (5 mg once daily 3 weeks on/1 week off) 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 Section 4.4.

Hypertension
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of hypertension was 47.1% (Grade ≥3 incidence: 18.4%) including three cases of hypertensive crisis. The incidence of hypertension was 11.8% (Grade ≥3 incidence: 1.3%) amongst 391 patients receiving placebo in the same studies. Hypertension led to dose interruption in 3.1%; dose reduction in 3.7% and permanent discontinuation in 0.5% of patients receiving FRUZAQLA.

Haemorrhage
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of haemorrhage was 16.6% (Grade ≥3 incidence: 1.3%) including two fatal cases. The incidence of haemorrhage was 9.5% (Grade ≥3 incidence: 1%) amongst 391 patients receiving placebo in the same studies. Haemorrhage led to discontinuation in 0.9% of patients receiving FRUZAQLA.

Infections
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of infection was 18.2% (Grade ≥3 incidence: 4.6%). The incidence of infection was 12% (Grade ≥3 incidence: 3.6%) amongst 391 patients receiving placebo in the same studies. Infection led to discontinuation in 0.6% of patients receiving FRUZAQLA.

Gastrointestinal (GI) perforation or fistula
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of GI perforation events was 2.9% (including 1 fatal case in FRESCO-2). The incidence was 0.3% amongst patients receiving placebo in the same studies.

Hepatotoxicity
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of liver function test (LFT) abnormalities was 47.5% (Grade ≥3 incidence: 5.2%). The incidence of LFT abnormalities was 32.7% (Grade ≥3 incidence: 2.8%) amongst 391 patients receiving placebo in the same studies. Fatal LFT abnormalities were reported in 0.3% of patients in the FRUZAQLA arm and 0.8% in the placebo arm.

Proteinuria
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of proteinuria was 32.9% (Grade ≥3 incidence: 2.8%). The incidence of proteinuria was 15.1% (Grade ≥3 incidence: 0.5%) amongst 391 patients receiving placebo in the same studies. Proteinuria led to dose interruption in 5.9%; dose reduction in 3.2% and permanent treatment discontinuation in 1.8% of patients receiving FRUZAQLA.

PPES
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of PPES was 32.7% (Grade ≥3 incidence: 8.5%). The incidence of PPES was 3.1% (Grade ≥3 incidence: 0.3%) amongst 391 patients receiving placebo in the same studies. PPES led to dose interruption in 6.4%, dose reduction in 6.3%, and permanent treatment discontinuation in 0.5% of patients treated with FRUZAQLA.

Hypothyroidism

Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of hypothyroidism was 18.3% (Grade ≥3 incidence: 0.3%). The incidence of hypothyroidism was 1% (none Grade ≥3) amongst 391 patients receiving placebo in the same studies. No events led to dose reduction or discontinuation.

Pancreatic enzyme elevation
Amongst 781 patients with mCRC who received FRUZAQLA in randomised trials, the incidence of pancreatic enzyme elevation was 4.1% (Grade ≥3 incidence: 1.9%). The incidence of pancreatic enzyme elevation was 1.0% (none Grade ≥3) amongst 391 patients receiving placebo in the same studies. Pancreatic enzyme elevation led to dose interruption in 0.8%; dose reduction in 0.1% and permanent discontinuation in 0.3% of patients receiving FRUZAQLA.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The highest dose of FRUZAQLA studied in clinical studies was 6 mg per day. The effects of FRUZAQLA overdose are unknown, and there is no known antidote for FRUZAQLA overdose. In the event of an overdose, interrupt FRUZAQLA, general supportive measures should be undertaken and observe until clinical stabilisation.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EK04

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

VEGF-mediated endothelial cell proliferation, and tubular formation were inhibited by fruquintinib *in vitro*. *In vitro* and *in vivo* studies showed fruquintinib inhibited VEGF-induced VEGFR-2 phosphorylation. Fruquintinib was shown to inhibit tumour growth in tumour xenograft mouse models.

Cardiac electrophysiology
Significant prolongation of heart rate-corrected QT (QTc) interval (>20 milliseconds) was not observed at the recommended dosage of fruquintinib (in FRESCO-2). A concentration-QT analysis (N=205) based on data from FRESCO-2 did not detect an association between fruquintinib plasma concentrations and changes in QTc interval from baseline.

Clinical trials

Clinical efficacy and safety

The clinical safety (see section 4.8) and efficacy of FRUZAQLA plus best supportive care (BSC) was evaluated in two randomised, placebo-controlled, double-blind, phase III studies (FRESCO-2 and FRESCO) in patients with mCRC who had previously received oxaliplatin and irinotecan-based chemotherapies.

FRESCO-2 study

The efficacy of FRUZAQLA was evaluated in FRESCO-2 (NCT04322539): an international, randomised, double-blind, placebo-controlled study that enrolled 691 patients with mCRC who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; an anti-EGFR therapy (if RAS wild type); and trifluridine/tipiracil, regorafenib, or both. Patients with MSI-H or dMMR tumours must have previously received an immune checkpoint inhibitor, and patients with BRAF V600E mutant tumours must have previously received a BRAF inhibitor, if locally approved and available. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, left ventricular fraction ≤50%, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, urine protein ≥1 g/24h, or body weight <40 kg were ineligible. Randomisation was stratified by prior receipt of trifluridine/tipiracil and regorafenib (trifluridine/tipiracil only vs. regorafenib only vs. both), RAS mutational status (wild-type vs. mutant) and duration of metastatic disease (≤18 months vs. >18 months).

In addition to BSC, patients were randomised (2:1) to receive FRUZAQLA 5 mg orally once daily (N=461) for the first 21 days of each 28-day cycle or placebo orally once daily (N=230). Treatment continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival (OS) and an additional efficacy endpoint was progression-free survival (PFS) as determined by investigators according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1).

Among the 691 randomised patients, the median age was 64 years (range: 25 to 86), with 47% ≥65 years of age. Male patients comprised 56%, 81% of patients were White, 43% had an ECOG PS of 0, 57% had an ECOG PS of 1, and 63% had *RAS*-mutant tumours. Eighteen percent of the patients were enrolled in North America, 72% in Europe, and 10% in Asia Pacific (Japan and Australia) region.

The median duration of metastatic disease was 39 months (range: 6 months to 16.1 years). The median number of prior lines of therapy for metastatic disease was 4 (range: 2 to 16). All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Additionally, 96% of patients had received prior anti-VEGF therapy, 39% had received prior anti-EGFR therapy, 52% had received trifluridine/tipiracil, 8% had received regorafenib, 39% had received both trifluridine/tipiracil and regorafenib, 4.6% had received immunotherapy, and 2.3% had received a BRAF inhibitor.

The addition of FRUZAQLA to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC (see Table 5 and Figure 1).

FRESCO study

The efficacy of FRUZAQLA was initially evaluated in FRESCO (NCT02314819), a multicentre, randomised, double-blind, placebo-controlled study conducted in China that enrolled 416 patients with mCRC who had disease progression during or after prior treatment with fluoropyrimidine-,

oxaliplatin-, or irinotecan-based chemotherapy. Patients with ECOG PS ≥2, left ventricular fraction ≤50%, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, urine protein ≥1 g/24h, and body weight <40 kg were ineligible. Randomisation was stratified by prior use of VEGF inhibitor (yes vs. no) and KRAS gene status (wild-type vs. mutant).

In addition to BSC, patients were randomised (2:1) to receive FRUZAQLA 5 mg orally once daily (N=278) for the first 21 days of each 28-day cycle or placebo (N=138). Treatment continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was OS. Secondary efficacy endpoints included PFS as determined by investigators according to RECIST v1.

Among the 416 randomised patients, the median age was 56 years (range: 23 to 75), with 19% ≥65 years of age. Male patients comprised 61%, all patients were Asian, 27% had an ECOG PS of 0, 73% had an ECOG PS of 1, and 44% had KRAS mutant tumours.

The median number of prior lines of therapy for metastatic disease was 2 (range: 2 to 3). All patients had received prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. Additionally, 30% of patients had received prior anti-VEGF therapy, and 14% had received prior anti-EGFR therapy.

The addition of FRUZAQLA to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC (see Table 5 and Figure 2).

Table 5 Efficacy results from randomised studies FRESCO-2 and FRESCO

	FRESCO-2		**FRESCO**	
Endpoint	**FRUZAQLA N=461**	**Placebo N=230**	**FRUZAQLA N=278**	**Placebo N=138**
OS				
Median in months (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)
Hazard Ratio[1] (95% CI)	0.66 (0.55, 0.80)		0.65 (0.51, 0.83)	
p-value[2]	< 0.001		< 0.001	
PFS				
Median in months (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)	3.7 (3.7, 4.6)	1.8 (1.8, 1.8)
Hazard Ratio[1] (95% CI)	0.32 (0.27 - 0.39)		0.26 (0.21 - 0.34)	
p-value[2,3]	< 0.001		-	

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of patients; OS=overall survival; PFS=progression-free survival.
The median OS and PFS were calculated using the Kaplan-Meier method.
[1]The HR and its 95% CI were estimated using stratified Cox's proportional hazards model (accounting for the stratification factors), in which the treatment arm is the only covariate in the model.
[2]p-value (2-sided) was calculated using the stratified log-rank test to account for the stratification factors.
[3]p-value for the PFS analysis in FRESCO not included due to lack of multiplicity adjustment for this analysis.

Figure 1: Kaplan-Meier curve for overall survival in FRESCO-2

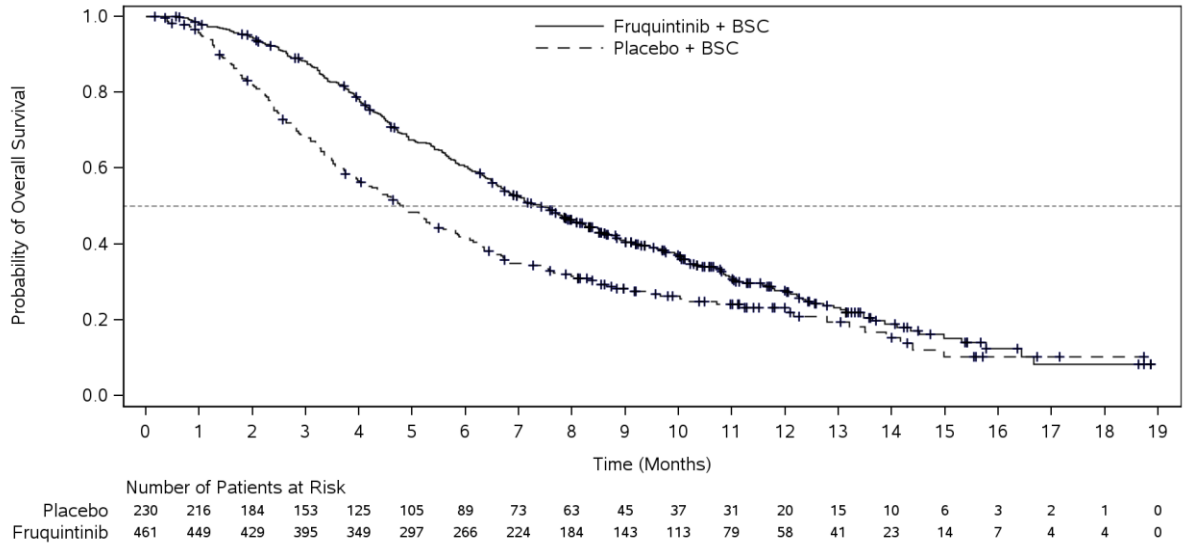
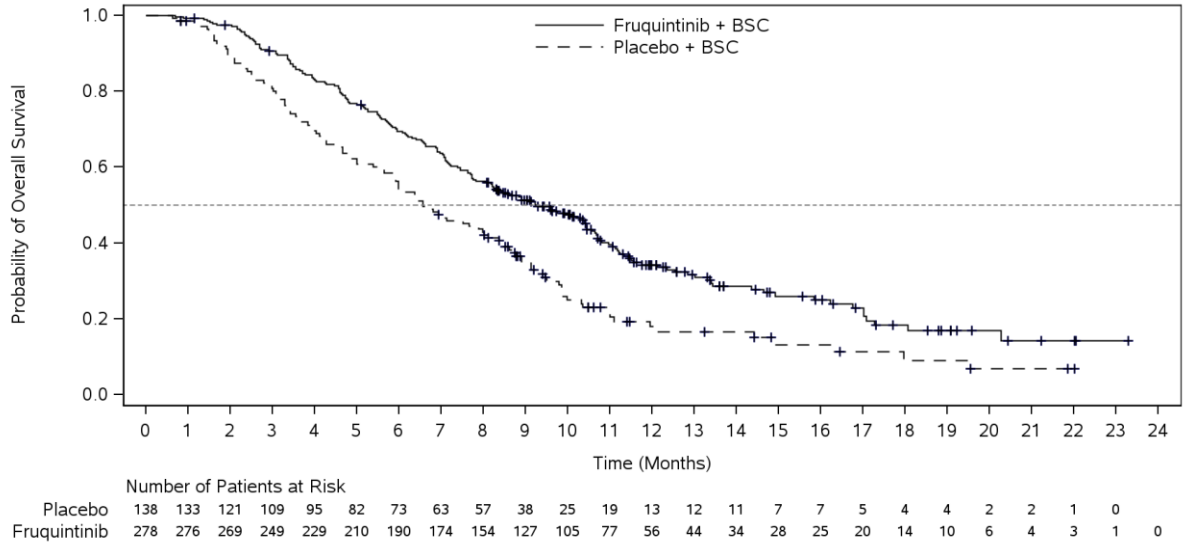


Figure 2: Kaplan-Meier curve for overall survival in FRESCO



5.2 PHARMACOKINETIC PROPERTIES

Absorption

At the recommended dosage (FRUZAQLA 5 mg once daily orally for the first 21 days of each 28-day cycle), fruquintinib exposure (maximum concentration [C_{max}] and area under the concentration-time curve for the dosing interval [$AUC_{0\text{-}24h}$]) is dose-proportional across the dose range of 1 to 6 mg (0.2 to 1.2 times the recommended dosage). The median (range) time from oral administration to C_{max} (T_{max}) is 2 (0-26) hours. Steady state fruquintinib serum concentration is achieved after 14 days, with a mean accumulation ratio (based on $AUC_{0\text{-}24h}$) of 4-fold. At the recommended dose, the geometric mean (%CV) steady-state fruquintinib C_{max} and $AUC_{0\text{-}24h}$ are 300 ng/mL (28%) and 5880 ng*h/mL (29%), respectively.

Effect of food

No clinically significant differences in fruquintinib pharmacokinetics were observed following administration of a high-fat meal. FRUZAQLA can be administered with or without food.

Distribution
The mean (SD) apparent volume of distribution of fruquintinib is approximately 46 (13) L. Plasma protein binding of fruquintinib is approximately 95%.

Metabolism
Fruquintinib is primarily eliminated by CYP450 and non-CYP450 (i.e., sulfation and glucuronidation) metabolism. CYP3A and to a lesser extent CYP2C8, CYP2C9, and CYP2C19 are the CYP450 enzymes involved in fruquintinib metabolism.

Excretion
The fruquintinib mean (SD) elimination half-life is approximately 42 (11) hours and the apparent clearance is 14.8 (4.4) mL/min.

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

Pharmacokinetics in special populations
No clinically significant differences in the pharmacokinetics of fruquintinib were observed based on age (18 to 82 years), sex, race/ethnicity, body weight (48 to 108 kg), renal impairment (CrCL 15 to 89 mL/min), or mild hepatic impairment (either total bilirubin ≤ ULN and AST > ULN; or total bilirubin >1 to 1.5 x ULN and any AST).

The effect of moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) on fruquintinib pharmacokinetics is unknown.

5.3 PRECLINICAL SAFETY DATA

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

Genotoxicity
No evidence of genotoxicity was observed in *in vitro* (bacterial reverse mutation assay and *in vitro* chromosomal aberrations assay in Chinese hamster ovary cells) and *in vivo* (rat micronucleus test with inclusion of an alkaline comet assay) studies.

Carcinogenicity
Carcinogenicity studies have not been conducted with fruquintinib.

Repeat dose toxicity
In repeat-dose toxicity studies in rats and dogs, the main target organ effects were identified in the gastrointestinal tract, hepatobiliary system, immune system, skeletal system, kidneys, hematopoietic system and adrenal gland at subclinical exposure levels or comparable exposure levels at the MRHD. All findings were reversible after a 4-week period without treatment, apart from the skeletal system (broken/lost teeth) and adrenal gland.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

<u>FRUZAQLA 1 mg hard capsules</u>

Inactive ingredients include maize starch, microcrystalline cellulose and purified talc. Capsule shells contain gelatin, titanium dioxide, tartrazine and sunset yellow FCF. The capsules are imprinted with TekPrint SW-9008 Black Ink (ARTG PI No 2328).

FRUZAQLA 5 mg hard capsules
Inactive ingredients include maize starch, microcrystalline cellulose and purified talc. Capsule shells contain gelatin, titanium dioxide, brilliant blue FCF and allura red AC. The capsules are imprinted with TekPrint SW-9008 Black Ink (ARTG PI No 2328).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

Refer to Section 4.5 for Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 ˚C. Protect from moisture. Keep bottle tightly closed. Do not remove desiccant cartridge from the bottle.

6.5 NATURE AND CONTENTS OF CONTAINER

FRUZAQLA 1 mg and 5 mg hard capsules
High density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure, containing 21 capsules of FRUZAQLA and desiccant cartridge. The HDPE bottle is packaged in a carton.

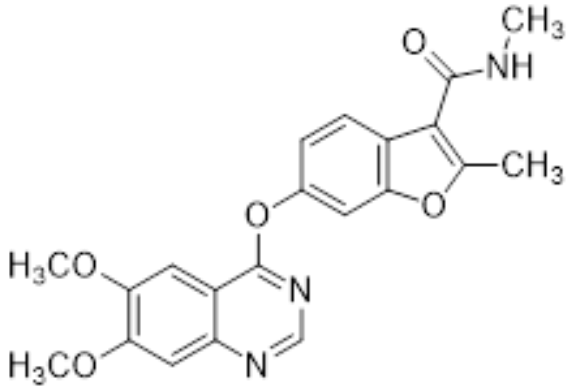
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Fruquintinib is a highly selective tyrosine kinase inhibitor.

Chemical structure
The chemical name for fruquintinib is 6-[(6,7-dimethoxyquinazolin-4-yl)oxy]-*N*,2-dimethyl-1-benzofuran-3- carboxamide. The molecular formula is C21H19N3O5, which corresponds to a molecular weight of 393.39 g/mol. The chemical structure is shown below:



Fruquintinib is a white to off-white powder with a dissociation constant (pKa) of 2.78. The aqueous solubility of fruquintinib is pH-dependent, with a solubility of 0.9 µg/mL at pH 6.8 that increases under acidic conditions to 129.9 µg/mL at pH 1.

CAS number
1194506-26-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

2 October 2024

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
	N/A – New PI