Indication	Monotherapy for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been previously treated with ruxolitinib and are unsuitable for momelotinib.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days continuously Continue until disease progression, unacceptable toxicity or patient choice. A formal medical review to review tolerability and whether treatment should continue or not should take place by at least the start of the third 4-weekly cycle of treatment.
Monitoring Parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • FBC, LFT (including amylase/lipase), blood urea nitrogen (BUN) and creatinine prior to treatment, monthly for the first 3 months, periodically throughout treatment and as clinically indicated. In the event of observed hepatic toxicity (elevated amylase, lipase, ALT and/or AST) monitor bloods every 2 weeks until resolution. • Baseline testing of thiamine (vitamin B1) levels, any deficiency should be correct prior to treatment. Levels should be taken monthly for the **first 3 months** of treatment and then every 3 months thereafter and as clinically indicated. • If baseline platelet count <50 x 10^9/L and ANC < 1.0 x 10^9/L, treatment should not be started. • Patients over 75 years of age should be closely monitored for toxicity and adverse events. • **Hepatic impairment:** No modification of the starting dose is required in mild, moderate and severe impairment. • **Renal impairment:** No dose adjustment required in mild to moderate renal impairment (CrCl 30 mL/min to 89 mL/min). Patients with pre-existing moderate renal impairment may require at least weekly monitoring and if necessary, dose modifications based on adverse reactions. In severe impairment (CrCl 15ml/min to 29ml/min) the dose should be reduced to 200mg OD. • **Management of adverse reactions and dose adjustments:** Refer to table one for dose modifications for haematologic toxicities, non-haematologic toxicities and management of Wernicke's encephalopathy (WE). • **Wernicke's encephalopathy (WE):** Cases of serious and fatal encephalopathy, including Wernicke's, were reported in patients taking fedratinib. Any change in mental status, confusion or memory impairment should prompt a full evaluation including a neurologic examination, assessment of thiamine levels and imaging. If encephalopathy is suspected, treatment should be discontinued immediately and parenteral thiamine treatment should be initiated while evaluating for all possible causes. • **Uveitis:** Fedratinib-associated uveitis is a late-onset adverse event, patients should be advised of the risk and common symptoms. No dose modifications are required for uveitis as long as effective topical corticosteroid treatment can control ocular inflammation. If uveitis does not respond to local ocular therapy, systemic treatment may be indicated and fedratinib should be withheld until resolution of ocular inflammation. • **Dose Modification:** Dosing interruption and/or dose reduction from the recommended initial dose of 400mg OD may be required based on individual safety and tolerability. (see table 1) • Treatment should be discontinued in patients who are unable to tolerate a dose of 200 mg daily.

	• If the adverse reaction that resulted in a dose reduction is controlled and the toxicity is resolved for at least 28 days, the dose level may be re-escalated to one dose level higher per month up to the original dose level. Dose re-escalation is not recommended if the dose reduction was due to a Grade 4 non-haematologic toxicity, >/=Grade 3 ALT, AST, or total bilirubin elevation, or reoccurrence of a Grade 4 haematologic toxicity. • **Supportive medication:** • Review TTOs and from cycle 2 prescribe loperamide, metoclopramide and ondansetron as required. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** • If concomitant use with a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin) cannot be avoided, the dose of fedratinib should be reduced to 200 mg. Patients should be carefully monitored weekly whist receiving concomitant therapy. If the strong CYP3A4 inhibitor is discontinued, the dose of fedratinib should be increased to 300 mg once daily for the first two weeks after discontinuation of the CYP3A4 inhibitor and then 400 mg once daily thereafter as tolerated. • Substrates that strongly or moderately induce CYP3A4 (e.g. phenytoin, rifampicin, efavirenz) and substrates that simultaneously inhibit CYP3A4 and CYP2C19 (e.g. fluconazole, fluvoxamine) or the combination of inhibitors of CYP3A4 and CYP2C19 should be avoided. • If fedratinib is co-administered with substrates of CYP3A4 (e.g. midazolam, simvastatin), CYP2C19 (e.g. omeprazole, S-mephenytoin) or CYP2D6 (e.g. metoprolol, dextromethorphan), dose modifications of co-administered medicines should be made as needed with close monitoring of safety and efficacy. • Co-administration with substrates that are renally excreted via organic cation transporter (OCT)2 and multidrug and toxin extrusion (MATE)1/2 K (e.g. metformin), caution should be exercised and dose modifications should be made as needed. • Grapefruit and grapefruit juice should be avoided during treatment. • **Missed dose:** If a dose is missed, the dose should be omitted and continue with the next scheduled dose. • **Pregnancy and contraception:** Females of reproductive potential should be advised to avoid becoming pregnant whilst receiving fedratinib and should use effective contraception during treatment and for at least 1 month after the last dose. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet. • **Driving and Machinery:** Fedratinib may cause dizziness, patients should refrain from driving or operating machinery if effected.
References	CDF list V1.382 accessed online 20.01.2026 SPC accessed online 28.01.2026 KMCC protocol HAEM-AML-036 V1

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Dose reductions for haematologic, non-haematologic treatment emergent toxicities and management of Wernicke's encephalopathy

Haematologic toxicity	**Dose reduction**
Grade 3 thrombocytopenia with active bleeding (platelet count < 50 x 10^9/L) or Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)	Interrupt until resolved to ≤ Grade 2 (platelet count < 75 x 10^9/L) or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 4 neutropenia (absolute neutrophil count [ANC] < 0.5 x 10^9/L)	Interrupt until resolved to ≤ Grade 2 (ANC < 1.5 x 10^9/L) or baseline. Restart dose at 100 mg daily below the last given dose. Granulocyte growth factors may be used at the physician's discretion.
Grade 3 and higher anaemia, transfusion indicated (haemoglobin level < 8.0 g/dL)	Interrupt until resolved to ≤ Grade 2 (haemoglobin level < 10.0 g/dL) or baseline. Restart dose at 100 mg daily below the last given dose.
Recurrence of a Grade 4 haematologic toxicity	discontinuation as per physician's discretion.
Non--haematologic toxicity	**Dose reduction**
≥ Grade 3 nausea, vomiting or diarrhoea not responding to supportive measures within 48 hours	Interrupt until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.
≥ Grade 3 ALT/ AST (> 5.0 to 20.0 x upper limit of normal [ULN]) or bilirubin (> 3.0 to 10.0 ULN)	Interrupt until resolved to ≤ Grade 1 (AST/ALT (> ULN - 3.0 x ULN) or bilirubin (> ULN - 1.5 x ULN)) or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST and bilirubin (total and direct) every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment.
≥ Grade 3 amylase / lipase (> 2.0 to 5.0 x ULN)	Interrupt until resolved to Grade 1 (> ULN - 1.5 x ULN) or baseline. Restart dose at 100 mg daily below the last given dose. Monitor amylase / lipase every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment.
≥ Grade 3 other non-haematologic toxicities	Interrupt until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.
Management of thiamine levels and Wernicke's encephalopathy	**Dose reduction**
For thiamine levels < normal range (74 to 222 nmol/L) * but ≥ 30 nmol/L without signs or symptoms of WE	Interrupt treatment. Dose with daily 100 mg oral thiamine until thiamine levels are restored to normal range*. Consider re-starting when thiamine levels are within normal range*.
For thiamine levels < 30 nmol/L without signs or symptoms of WE	Interrupt treatment. Initiate treatment with parenteral thiamine at therapeutic dosages until thiamine levels are restored to normal range*. Consider re-starting when thiamine levels are within normal range*.
For signs or symptoms of WE regardless of thiamine levels	Discontinue treatment and immediately administer parenteral thiamine at therapeutic dosages.

*the normal thiamine range may differ depending on the methods used by the laboratory.

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**FEDRATINIB**	**400mg**	PO	OD Swallow whole, do not chew or open the capsules. Taking with a high fat meal may help reduce nausea and vomiting. Available as 100mg capsule
	Thiamine	100mg	PO	OD
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Supply with cycle 1 and cycle 2 then only if required.
	Ondansetron	8mg	PO	BD for up to 5 days when required as directed. Supply with cycle 1 and cycle 2 then only if required.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.