Fedratinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of disease-related splenomegaly or symptoms in adult patients with: primary myelofibrosis (PMF), post polycythaemia vera myelofibrosis (PVMF) or post essential thrombocythaemia myelofibrosis (ET MF) who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib	 D47 D45 D47	00788a	CDS - 01/12/2022

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Fedratinib is administered orally once daily on a continuous basis until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Diluent & Rate	Cycle
Fedratinib	400mg once daily	PO	N/A	Continuous, every 28 days
If a dose is missed, the next scheduled dose should be taken the following day. Extra capsules should not be taken to make up for the missed dose.				
The capsules should not be opened, broken or chewed. They should be swallowed whole, preferably with water, and may be taken with or without food. However, administration with a high fat meal may reduce the incidence of nausea and vomiting, therefore it is recommended to be taken with food.				

Note: Transitioning from ruxolitinib to fedratinib:

If transitioning directly from ruxolitinib to fedratinib, there is a risk of withdrawal reaction after sudden discontinuation of ruxolitinib, particularly in the setting of proliferative myelofibrosis.

- To minimize the risk of withdrawal reaction, the dose of ruxolitinib should be gradually reduced by 5mg twice daily every 3 days over 2 weeks (see Table 1).
- In higher risk proliferative patients, consider the use of corticosteroids during the transition period (e.g. 0.5mg/kg prednisolone for 2 weeks with a taper) or commencing gradual reduction of ruxolitinib dosing above during the first two weeks of fedratinib dosing.

Table 1: Recommended dose reduction of ruxolitinib to avoid withdrawal reaction

Day (of 2 week withdrawal period)	Ruxolitinib dose
Days 1-3	25mg twice daily
Days 4-6	20mg twice daily
Days 7-9	15mg twice daily
Days 10-12	10mg twice daily
Days 13-14	5mg twice daily
Day 15	Discontinue

ELIGIBILITY:

- Indications as above
- ≥ 18 years
- ECOG 0-2
- Adequate hepatic and renal function

CAUTION:

Use with caution in:

- Fedratinib should not be started in patients with thiamine deficiency, until thiamine levels have been corrected. Thiamine levels should be monitored throughout treatment due to the risk of Wernicke's encephalopathy **(See Premedication below)**.

EXCLUSIONS:

- Hypersensitivity to fedratinib or to any of the excipients
- Prior history of chronic liver disease
- Pregnancy/breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Thiamine levels
- Physical exam including splenic measurement by palpation
- Weight
- Amylase/lipase
- Blood glucose
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile every 2 weeks for the first 6 weeks, then every 4 weeks thereafter
- Thiamine levels every 4 weeks for the first 3 cycles, then every 3 months in stable patients
- Physical exam including splenic measurement by palpation if clinically indicated
- Amylase/lipase every 4 weeks for the first 3 cycles, then every 3 months in stable patients
- Blood glucose if clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose modifications for haematologic toxicities, non-haematologic toxicities and management of Wernicke's encephalopathy (WE) are shown in Tables 3, 5 and 6.
- Dose re-escalation: If the adverse reaction due to fedratinib that resulted in a dose reduction is controlled with effective management 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 alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin elevation, or reoccurrence of a Grade 4 haematologic toxicity.

Table 2: Recommended dose reductions for all toxicities

Dose Level	Dose
Recommended dose	400mg/day
First dose reduction (Dose level -1)	300mg/day
Second dose reduction (Dose level -2)	200mg/day*
***If further dose reduction below 200mg/day is required, discontinue treatment**	

Haematological:

Table 3: Dose modifications for haematologic toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥ 0.5	**and**	≥ 50	100%
< 0.5	**or**	< 50 (with active bleeding), or < 25	Delay until ANC ≥ 1.0 $x10^9$/L and platelets ≥ 50 $x10^9$/L. Restart at the next lower dose level.

Renal and Hepatic Impairment:

Table 4: Dose modification of fedratinib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Cr Cl (ml/min)	**Dose**	**Impairment**	**Dose**
30-89 (mild – moderate)	No modification of starting dose recommended.	Mild to moderate.	No modification of starting dose recommended.
15-29 (severe)	Reduce dose to 200mg. Monitor for toxicity.	Child-Pugh class C or total bilirubin >3 x ULN and any AST increase (Severe).	Avoid
Due to potential increase of exposure, patients with pre-existing moderate renal impairment may require at least weekly safety monitoring and if necessary, dose modifications based on adverse reactions.			

Management of adverse events:

Table 5: Dose modifications for non-haematologic treatment emergent toxicities

Toxicity	Dose reduction
≥ Grade 3 nausea, vomiting or diarrhoea not responding to supportive measures within 48 hours	Interrupt fedratinib dose 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 ULN) or bilirubin (> 3.0 to 10.0 ULN)	Interrupt fedratinib dose 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 with fedratinib.
≥ Grade 3 amylase / lipase (> 2.0 to 5.0 x ULN)	Interrupt fedratinib dose 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 with fedratinib.
Grade 3 other non-haematologic toxicities	Interrupt fedratinib dose until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.

Table 6: Management of thiamine levels and Wernicke's encephalopathy (WE)

Thiamine levels	Dose reduction
For thiamine levels < normal range (74 to 222 nmol/L)* but ≥ 30 nmol/L without signs or symptoms of WE	Interrupt fedratinib treatment. Dose with daily 100 mg oral thiamine until thiamine levels are restored to normal range*. Consider re-starting fedratinib treatment when thiamine levels are within normal range*.
For thiamine levels < 30 nmol/L without signs or symptoms of WE	Interrupt fedratinib treatment. Initiate treatment with parenteral thiamine at therapeutic dosages until thiamine levels are restored to normal range*. Consider re-starting fedratinib treatment when thiamine levels are within normal range*.
For signs or symptoms of WE regardless of thiamine levels	Discontinue fedratinib treatment and immediately administer parenteral thiamine at therapeutic dosages.

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

Dose modifications with concomitant use of strong CYP3A4 inhibitors:

- If concomitant strong CYP3A4 inhibitors cannot be avoided, the dose of fedratinib should be reduced to 200 mg. Patients should be carefully monitored (e.g. at least weekly) for safety.
- In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, the fedratinib dose should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor and then 400 mg once daily thereafter as tolerated.
- Additional dose adjustments should be made as needed, based upon monitoring of fedratinib-related safety and efficacy.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Fedratinib: Moderate to High **(Refer to local policy)**

PREMEDICATIONS:

- Consideration should be given to co-administration of thiamine supplementation if thiamine monitoring is impractical.
- It is recommended that prophylactic anti-emetics be used **(Refer to local policy)** for the first 8 weeks of treatment and continued thereafter as clinically indicated.

OTHER SUPPORTIVE CARE:

- Anti-diarrhoeal treatment throughout fedratinib treatment **(Refer to local policy).**
- Thiamine supplementation **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Encephalopathy, including Wernicke's encephalopathy:** Cases of serious and fatal encephalopathy, including Wernicke's, were reported in patients taking fedratinib. Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes and ophthalmoplegia (e.g. nystagmus, diplopia). Any change in mental status, confusion or memory impairment should raise concern for potential encephalopathy, including Wernicke's and prompt a full evaluation including a neurologic examination, assessment of thiamine levels and imaging. If encephalopathy is suspected, fedratinib treatment should be discontinued immediately and parenteral thiamine treatment should be initiated while evaluating for all possible causes (refer to Table 6). Patients should be monitored until symptoms have resolved or improved and thiamine levels have normalised.
- **Anaemia, thrombocytopenia and neutropenia:** Treatment with fedratinib may cause anaemia, thrombocytopenia and neutropenia. Complete blood counts should be obtained at baseline, periodically during treatment and as clinically indicated. Fedratinib has not been studied in patients with a baseline platelet count < 50 x 10^9/L and ANC < 1.0 x 10^9/L.
    - Anaemia generally occurs within the first 3 months of treatment. Patients with a haemoglobin level below 10.0 g/dL at the start of therapy are more likely to develop anaemia of Grade 3 or above during treatment and should be carefully monitored (e.g. once weekly for the first month until haemoglobin levels improve). Patients developing anaemia may require blood transfusions. Consider dose reduction for patients developing anaemia particularly for those who become red blood cell transfusion dependent.

  - Thrombocytopenia generally occurs within the first 3 months of treatment. Patients with low platelet counts (< 100 x 10^9/L) at the start of therapy are more likely to develop thrombocytopenia of Grade 3 or above during treatment and should be carefully monitored (e.g. once weekly for the first month until platelet count improves). Thrombocytopenia is generally reversible and is usually managed by supportive treatment such as dose interruptions, dose reduction and/or platelet transfusions if necessary. Patients should be made aware of the increased risk of bleeding associated with thrombocytopenia.
  - Neutropenia was generally reversible and was managed by temporarily withholding fedratinib.
- **Gastrointestinal events**: Nausea, vomiting and diarrhoea are among the most frequent adverse reactions in fedratinib-treated patients. Most of the adverse reactions are Grade 1 or 2 and typically occur within the first 2 weeks of treatment. Consider providing appropriate prophylactic anti-emetic therapy (e.g. 5-HT3 receptor antagonists) during fedratinib treatment. Diarrhoea should be treated with anti-diarrheal medicinal products promptly at the first onset of symptoms. For cases of Grade 3 or higher nausea, vomiting, and diarrhoea that are not responsive to supportive measures within 48 hours, refer to Table 5 for recommended management.
- **Hepatic toxicity**: Elevations of ALT and AST have been reported with fedratinib treatment and one case of hepatic failure was reported. Patients should have their hepatic function monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. After observed toxicity, patients should be monitored at least every 2 weeks until resolution. ALT and AST elevations were generally reversible with dose modifications or permanent treatment discontinuation.
- **Elevated amylase/lipase**: Elevations of amylase and/or lipase have been reported with fedratinib treatment and one case of pancreatitis was reported. Patients should have their amylase and lipase monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. After observed toxicity, patients should be monitored at least every 2 weeks until resolution. For Grade 3 or higher amylase and/or lipase, dose modifications are recommended (refer to Table 5).
- **Elevated creatinine**: Elevations of creatinine have been reported with fedratinib treatment. Patients should have their creatinine levels monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated**.**
- **Women of childbearing potential/Contraception**: Females of reproductive potential should be advised to avoid becoming pregnant whilst receiving fedratinib and should use effective contraception during treatment with fedratinib and for at least 1 month after the last dose.

DRUG INTERACTIONS:

- Concomitant administration of fedratinib with strong CYP3A4 inhibitors increases fedratinib exposure. Increased exposure of fedratinib may increase the risk of adverse reactions. If strong CYP3A4 inhibitors cannot be replaced, the dose of fedratinib should be reduced when administering with strong CYP3A4 inhibitors, (e.g. ketoconazole, ritonavir). Patients should be carefully monitored (e.g. at least weekly) for safety.
- Prolonged co-administration of a moderate CYP3A4 inhibitor may require close safety monitoring and if necessary, dose modifications based on adverse reactions.
- Agents that simultaneously inhibit CYP3A4 and CYP2C19 or the combination of inhibitors of CYP3A4 and CYP2C19 may increase fedratinib exposure and should be avoided in patients receiving fedratinib.
- Agents that strongly or moderately induce CYP3A4 (e.g. can decrease fedratinib exposure and should be avoided in patients receiving fedratinib.

- If fedratinib is to be co-administered with substrate 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.
- If fedratinib is to be co-administered with agents 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.
- The concomitant use of haematopoietic growth factors with fedratinib has not been studied. The safety and efficacy of these co-administrations are not known.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	01/12/2022		Dr Clodagh Keohane

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