Fedratinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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

* This is for post 2012 indications only.

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:

- Direct swap is advised when switching from ruxolitinib to fedratinib.
- There is a risk of withdrawal reaction after sudden discontinuation of ruxolitinib, particularly in the setting of proliferative myelofibrosis.
- Consider ruxolitinib taper or short-course prednisolone in patients on ≥20mg BD ruxolitinib or significant constitutional symptoms.

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 Premedications below)**.
- Prior history of chronic liver disease

EXCLUSIONS:

- Hypersensitivity to fedratinib or to any of the excipients
- 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
- Amylase/lipase
- Blood glucose
- Physical exam including splenic measurement by palpation
- Weight
- 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 2, 3, 4 and 5
- 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 1: 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 2: 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 3: Dose modification of fedratinib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
CrCl (mL/minute)	**Dose**	**Impairment**	**Dose**
≥30	No dose adjustment is needed		
15-30	50% of the original dose	No modification of the starting dose is required for patients with mild, moderate and severe hepatic impairment, based on the Child-Pugh classification.	
Haemodialysis	50% of the original dose		
Renal – Giraud et al (2023) Hepatic – Summary of Product Characteristics			

Management of adverse events:

Table 4: 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 x 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 5: 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:

As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

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

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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.

PREMEDICATIONS:

- Consideration should be given to co-administration of thiamine supplementation if thiamine monitoring is impractical.

OTHER SUPPORTIVE CARE:

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

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

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

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.
- **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 5). 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 4 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 4).
- **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:

- Current SmPC and drug interaction databases should be consulted for more information.

REFERENCES:

1. Pardanani A et al. Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2015 Aug; 1(5):643-51. doi: 10.1001/jamaoncol.2015.1590. PMID: 26181658.
2. Pardanani A et al. Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis. Br J Haematol. 2021 Oct; 195(2):244-248. doi: 10.1111/bjh.17727. Epub 2021 Jul 30. PMID: 34331348; PMCID: PMC9292894.
3. Harrison CN et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol. 2017 Jul; 4(7):e317-e324. doi: 10.1016/S2352-3026(17)30088-1. Epub 2017 Jun 8. PMID: 28602585; PMCID: PMC8207822.
4. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. Fedratinib Summary of Product Characteristics EMA. Last updated 18/07/2024. Accessed 08/03/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/inrebic-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/12/2022		Dr Clodagh Keohane
2	06/11/2024	Regimen reviewed: • Updated advice when transitioning from ruxolitinib to fedratinib in treatment text and removed Table 1. • Updated Cautions and Exclusions • Updated Table 3: Dose modification of fedratinib in renal and hepatic impairment to align with Giraud et al (2023) [renal] and SmPC [hepatic] • Updated Supportive care, Adverse effects/Regimen specific complications and Drug Interactions sections to align with NCCP standard wording.	Dr Clodagh Keohane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.