

Ruxolitinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of disease-related splenomegaly or symptoms in adult patients with: Primary myelofibrosis (chronic idiopathic myelofibrosis)	D47	00229a	CDS
Post polycythaemia vera myelofibrosis	D45	00229b	CDS
Post essential thrombocythaemia myelofibrosis	D47	00229c	CDS

**If the reimbursement status is not defined¹, the indication has yet to be assessed through the formal HSE reimbursement process.*

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.

Ruxolitinib is administered on a continuous basis twice daily until disease progression or unacceptable toxicity develops. Discontinue if no reduction of spleen size or improvement of constitutional symptoms at 6 months.

It is recommended that for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

Drug	Platelets (x10 ⁹ /L) ^a	Starting dose ^b	Maintenance Dose	Route
Ruxolitinib	>200	20mg BD	Adjust according to platelet (max 25mg BD)	PO with or without food
	100-200	15mg BD		
	50-99 ^c	5mg BD		
^a plus ANC 1.0 x 10 ⁹ /L ^b Consider lower starting dose (followed by optional upwards dose titration for patients unable to tolerate a decline in haemoglobin. ^c Limited information available for this group. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.				
If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.				

ELIGIBILITY:

- Indications as above-Patients with INT -2 and high risk disease with symptomatic splenomegaly or constitutional symptoms.
- ECOG status 0-3

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EXCLUSIONS:

- Eligible for allogeneic stem cell transplant
- Pregnancy or lactation.
- Hypersensitivity to ruxolitinib or any of the excipients.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- Physical exam including splenic measurement by palpation
- Weight
- ECG, blood pressure

Regular tests:

- FBC every 1-2 weeks for first 3 months, every 2-4 weeks for 3-6 months. After 6 months of therapy every 1-3 months.
- Renal and liver profile as clinically indicated.
- Physical exam including splenic measurement by palpation
- Weight
- ECG, blood pressure.

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.
- The starting dose should not be increased within the first 4 weeks of treatment and thereafter not more frequently than at 2-week intervals.
- DOSE ESCALATION: If efficacy is regarded as insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5mg twice daily. The maximum dose of ruxolitinib is 25mg twice daily.

Haematological:

Table1: Dose modification of ruxolitinib in haematological toxicity

ANC ($\times 10^9$ /L)		Platelets ($\times 10^9$ /L)	Dose
<0.5	and/or	<50	Interrupt treatment. After recovery, dosing may be restarted at 5mg BD and gradually increased based on FBC monitoring.
		50-100	Consider dose reduction to avoid dose interruptions for thrombocytopenia.

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For ANC 0.5 to 1.0 x 10⁹/L the dose of ruxolitinib may be modified according to table below.

Existing dose	New dose		
	Platelets (x 10 ⁹ /L) 100-125	Platelets (x 10 ⁹ /L) 75-99	Platelets (x 10 ⁹ /L) 50-74
25mg BD	20mg BD	10mg BD	5mg BD
20mg BD	15mg BD	10mg BD	5mg BD
15mg BD	15mg BD	10mg BD	5mg BD
10mg BD	10mg BD	10mg BD	5mg BD
5mg BD	5mg BD	5mg BD	5mg BD

Renal and Hepatic Impairment:

Table 2: Dose modification of ruxolitinib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment
Cr Cl (ml/min)	Recommended dose	In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily
>30	Dose as per treatment table	
<30	Reduce recommended starting dose based on platelet count by approximately 50% to be administered daily.	

Table 3: Dose modification of ruxolitinib in patients receiving dialysis

Platelet count (x 10 ⁹ /L)	Recommended dose
>200	20 mg single daily dose (or two doses of 10 mg) following each dialysis session
100-200	15 mg single daily dosing following each dialysis session

CYP3A4 inhibitors or fluconazole:

- When ruxolitinib is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of ruxolitinib should be reduced by approximately 50% to be administered twice daily. The use of ruxolitinib and fluconazole at doses greater than 200mg daily should be avoided. Patients on ruxolitinib and receiving strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy.
- For weak to moderate inducers consider alternative therapies where possible, dose adjustment not required.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS:

None required

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OTHER SUPPORTIVE CARE:

None Required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

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

- **Myelosuppression:** Anaemia, thrombocytopenia and neutropenia are dose related adverse effects to treatment with ruxolitinib. Patients with low platelet counts ($< 200 \times 10^9/L$) at the start of treatment are more likely to develop thrombocytopenia during treatment. It is usually reversible and managed by reducing the dose or temporarily withholding treatment. However platelet transfusions may be required as clinically indicated. Patients with a haemoglobin level $< 10g/dl$ at the beginning of treatment have a higher risk of developing a haemoglobin level $< 8g/dl$ during treatment. More frequent monitoring of haematology parameters and of clinical signs and symptoms of ruxolitinib-related adverse drug reactions are recommended for patients with baseline haemoglobin $< 10g/dl$.
- **Infections:** Therapy should not be started until active serious infections have resolved. Any signs or symptoms of infections while being treated with ruxolitinib should be treated promptly.
- **Herpes Zoster:** Patients should be educated about early signs and symptoms of herpes zoster advising that treatment should be sought as early as possible.
- **Progressive multifocal leukoencephalopathy (PML):** Use of ruxolitinib may be associated with an increased risk of PML. Patients must be monitored for any new or worsening neurological symptoms. If PML is diagnosed treatment with ruxolitinib should be discontinued.
- **Non-melanoma skin cancer :** Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.
- **Arrhythmia:** A decrease in heart rate and prolongation of PR interval was noted on ECG in ruxolitinib treated patients. The clinical significance of these findings remains unclear.
- **Withdrawal effects:** Following interruption or discontinuation of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness. Unless abrupt discontinuation is required, gradual tapering of the dose of ruxolitinib may be considered though the utility of tapering is unproven. Cover with systemic steroids has also been used in these circumstances. (Harrison 2013)

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Ruxolitinib is eliminated through metabolism catalyzed by CYP3A4 and CYP2C9. Thus medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure (Reference Dose Modifications above). Patients should be counselled to avoid grapefruit and grapefruit juice.

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

ATC CODE:

Ruxolitinib - L01XE18

REFERENCES:

1. Verstovsek S, Mesa RA et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med* 2012;366(9):799-807
2. Harrison C, Kiladjian JJ et al JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med* 2012;366(9):787-98
3. Jakavi® Summary of Product Characteristics Accessed January 2016 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002464/WC500133223.pdf
4. Harrison, C., Mesa, R. et al Practical management of patients with myelofibrosis receiving ruxolitinib. *Expert Rev Hematol.* 2013: 6(5): 511-523.

Version	Date	Amendment	Approved By
1	18/02/2014	Initial Draft	Dr Eibhlin Conneally
2	03/05/2016	Updated dosing in renal impairment, adverse reactions	Dr Eibhlin Conneally
3	12/9/2016	Updated dosing with CYP3A4 inhibitors or fluconazole based on changes to SmPC	Dr Eibhlin Conneally
4	15/11/2018	Updated to new NCCP template.	Dr Eibhlin Conneally

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at; <http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/>

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