Variability in UK myelofibrosis care[1–3]

Myelofibrosis

Real-world insights from REALISM UK[1,2] and findings from a physician survey on the use of the 2012 BSH guidelines for the diagnosis and management of MF in the UK[3]

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References: 1. Mead A, et al. Ther Adv Hematol. 2022;13:1–15. **2.** Mesa R, et al. BMC Cancer. 2016;16;167. **3.** Harrison CN, et al. Br J Haematol. 2020;188:e80–e112. **4.** Novartis Pharmaceuticals NI Ltd. JAKAVI® summary of product characteristics. Last accessed July 2024.

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JAKAVI® ruxolitinib

JAKAVI® is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis. JAKAVI® is also indicated for adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.[4]

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report or alternatively email medinfo.uk@novartis.com or call 01276 698370.

REALISM UK: Addressing the lack of real-world data on the MF treatment pathway[1]

Experts agree that current variances in MF patient care often result in a lack of clear treatment pathways for patients in the real world.[1]

There are a number of treatment options available for patients with MF, most of which only relieve symptoms and are not disease-modifying.[1] This means that there is no unifying treatment for patients with MF, and quality of care can vary across the UK.

Mapping the MF treatment pathway is critical to understanding treatment barriers and to help improve patient management for people with MF.[1]

REALISM UK: a retrospective, multicentre, non-interventional study of MF treatment practices in 15 UK centres[1]

Medical record data were collected from 200 patients.

The primary endpoint of the study was the time period elapsing between initial diagnosis of MF and commencement of first active intervention for MF. The key secondary endpoints were the distribution of patient characteristics at the time of MF diagnosis. Other secondary endpoints included the frequency of anaemia, thrombocytopenia, and serious infections.[1]

Clinical characteristics[1]

The three most common symptoms were:[1]

- **27%** Fatigue (n=54/200)
- **21%** Weight loss (n=42/200)
- **16%** Night sweats (n=31/200)

Eligibility criteria:[1]

- Aged ≥18 at time of diagnosis with MF
- MF diagnosis >6 months and <5 years prior to data collection
- ≥1 follow-up visit

MF management strategies included:[1]

- JAKAVI®
- Hydroxycarbamide
- Watch and wait
- Stem cell transplant
- Combination strategies
- Interferon-α
- JAK inhibitor (part of clinical trial)

Reference: 1. Mead A, et al. Ther Adv Hematol. 2022;13:1–15.

REALISM UK: 1 in 2 patients with intermediate-2 or high-risk MF failed to receive active treatment as an initial management strategy[1]

Throughout the REALISM UK study, watch and wait was the most commonly used overall management strategy (67%) for patients with MF regardless of risk stratification (N=200).[2]

Risk stratification is an important factor for determining management strategies and the time taken to initiate treatment.[1]

The REALISM UK study found that at diagnosis, **49%** of patients were classified with intermediate-2 or high-risk disease according to the IPSS. Prognostic scoring appeared to be poorly recorded in patient notes,[1] with at least one scoring item unavailable in **14.5%** of patients.[1]

Of patients who were stratified according to prognostic risk, **49%** of patients classified as intermediate-2, and **46%** of patients classified as high-risk were initially managed with watch and wait.[1]

Choice of first management strategy by IPSS group[1]

First management strategy	Low (0) (n=15)	Intermediate-1 (n=58)	Intermediate-2 (n=59)	High ≥3 (n=39)
	n (%)	n (%)	n (%)	n (%)
Anagrelide	0 (0%)	1 (2%)	1 (2%)	1 (3%)
Clinical trial – other JAK-1	0 (0%)	0 (0%)	2 (3%)	0 (0%)
Hydroxycarbamide + anagrelide	0 (0%)	1 (2%)	2 (3%)	0 (0%)
Hydroxycarbamide	4 (27%)	10 (17%)	11 (19%)	10 (26%)
Interferon-α	0 (0%)	2 (3%)	1 (2%)	0 (0%)
Ruxolitinib	1 (7%)	9 (16%)	13 (22%)	10 (26%)
Watch and wait	**10 (67%)**	**35 (60%)**	**29 (49%)**	**18 (46%)**

Management strategies for patients for whom IPSS scoring was not available (n=29) are not shown in this table.

Despite presenting with symptomatic disease

53.5% of patients with MF did not receive active treatment as their initial management strategy.[1]

Clinical implications

Proactive identification of patients eligible for active management is critical to decrease the detrimental impact of MF on patients' QoL.[3–10]

References:

1. Mead A, et al. Ther Adv Hematol. 2022;13:1–15.
2. Mead A, et al. Ther Adv Hematol. 2022;13:1–15. Supplementary Table 2.
3. Mesa R, et al. BMC Cancer. 2016;16;167.
4. Vannucchi A, et al. Haematologica. 2015;100:1139–1145.
5. Vannucchi A, et al. Ann Oncol. 2015;26:85–99.
6. Scottish Medicines Consortium. Ruxolitinib (Jakavi). Available at: https://www.scottishmedicines.org.uk/medicines-advice/ruxolitinib-jakavi-fullsubmission-86713/. Last accessed July 2024.
7. Verstovsek S, et al. N Engl J Med. 2012;366:799–807.
8. Harrison C, et al. N Engl J Med. 2012;366:787–798.
9. McLornan DP, et al. Br J Haematol. 2024;204:136–150.
10. National Institute for Health and Care Excellence. Technology appraisal guidance [TA386]. Available at: https://www.nice.org.uk/guidance/ta386. Last accessed July 2024.

Actively manage your patients with MF and help preserve their QoL by identifying those eligible for JAKAVI®[1,2]

REALISM UK showed that many patients did not have their prognostic risk scores documented and failed to receive active management when clinically indicated.[3]

Help improve access to treatment by identifying eligible patients at diagnosis and during monitoring, according to clinical guidelines.[4–9]

At diagnosis

Use the IPSS to identify a patient's MF risk category to inform your choice of first management strategy.[4,5]

NICE
National Institute for Health and Care Excellence

JAKAVI® is recommended as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis, only in people with intermediate-2 or high-risk disease, and if the company provides JAKAVI® with the discount agreed in the patient access scheme.[4]

Scottish Medicines Consortium

JAKAVI® is also accepted for use in Scotland for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis.[6]

During monitoring

Continually monitor your patients' symptoms to identify progression and initiate treatment as soon as they are eligible.[4,6,7]

BSH

JAKAVI® is recommended as an option for patients with myelofibrosis-related splenomegaly or symptoms.[7]

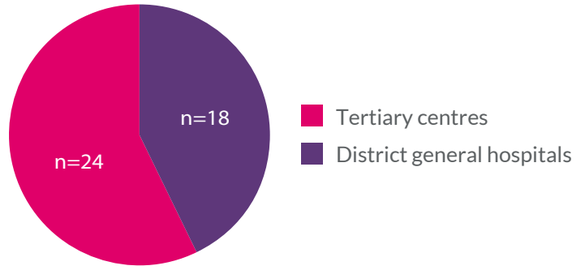
Recommendation from the 2024 BSH guidelines.

References:
1. Verstovsek S, et al. N Engl J Med. 2012;366:799–807.
2. Harrison C, et al. N Engl J Med. 2012;366:787–798.
3. Mead A, et al. Ther Adv Hematol. 2022;13:1–15.
4. National Institute for Health and Care Excellence. Technology appraisal guidance [TA386]. Available at: https://www.nice.org.uk/guidance/ta386. Last accessed July 2024.
5. Vannucchi A, et al. Ann Oncol. 2015;26:85–99.
6. Scottish Medicines Consortium. Ruxolitinib (Jakavi). Available at: https://www.scottishmedicines.org.uk/medicines-advice/ruxolitinib-jakavi-fullsubmission-86713/. Last accessed July 2024.
7. McLornan DP, et al. Br J Haematol. 2024;204:136–150.
8. Novartis Pharmaceuticals NI Ltd. JAKAVI® summary of product characteristics. Last accessed July 2024.
9. Vannucchi A, et al. Haematologica. 2015;100:1139–1145.

Findings from a physician survey on the use of the 2012 BSH guidelines for the diagnosis and management of MF in the UK[1]

In order to understand how BSH guidelines for the diagnosis and management of patients with MF are used in daily practice, face-to-face interviews were carried out with haematologists between September and October 2018.[1]

42 consultant haematologists completed the survey[1]

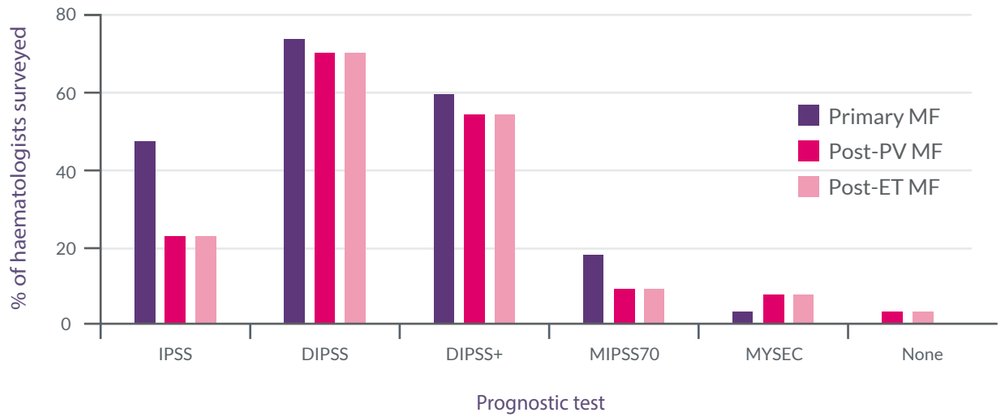


Diagnostic and prognostic testing[1]

The study found that diagnostic assessments were fairly consistent, with **88.1%** of haematologists having access to a next-generation sequencing (NGS) panel or equivalent. That being said, **64.3%** wanted further education on interpreting NGS panels and **48.9%** reported that they did not feel comfortable interpreting the results.[1]

Haematologists also used various prognostic tests in MF, although **95.3%** of haematologists use DIPSS and/or DIPSS Plus prognosis tools for primary MF.[1]

Choice of prognostic tests varied in MF[1]



Adapted from Harrison CN, et al. 2020.[1]

Some physicians reported using more than one prognostic tool for each category.[1]

Reference: 1. Harrison CN, et al. Br J Haematol. 2020;188:e80–e112.

Haematologists have access to different management tools, which was reflected in survey results[1]

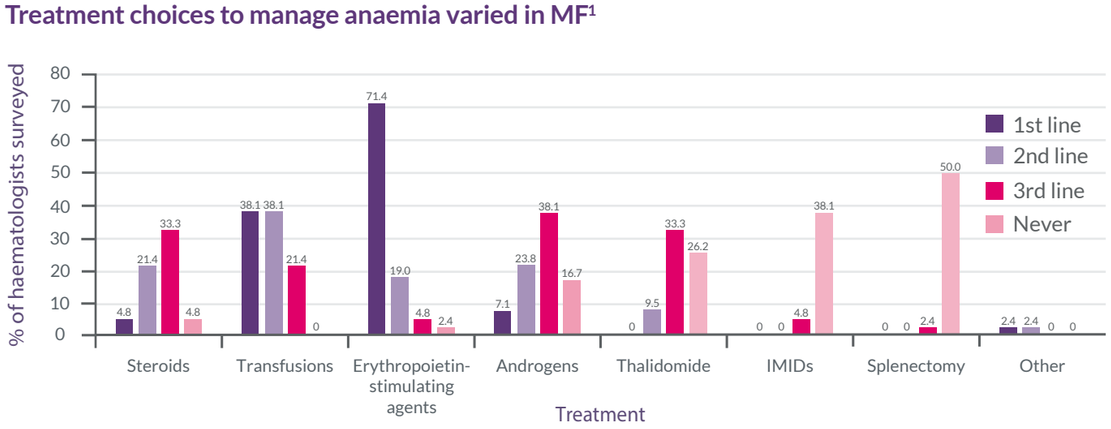
Symptom assessment, first-line treatment strategies and the management of anaemia[1]

Only **52.4%** of haematologists used symptom assessment tools, predominantly to track treatment responses, whilst only **35.7%** utilised these tools to guide treatment initiation.[1] Of those who did use symptom assessment tools, **79.2%** used the MPN10 symptom tracker.[1]

Hydroxycarbamide was the most commonly prescribed **(73.8%)** first-line treatment for hyperproliferation, followed by JAK inhibitors **(45.2%)**, although the proportion of patients treated with JAK inhibitors varied widely among haematologists, from **30–40%** to **>80%**.[1]

Treatment choices for the management of anaemia were also varied, with **71.4%** of haematologists using erythropoietin-stimulating agents first line – as recommended by the guidelines. The use of steroids and thalidomide were also reported, despite not being in agreement with guidelines.[1]

Treatment choices to manage anaemia varied in MF[1]



Adapted from Harrison CN, et al. 2020.[1]

Some physicians reported using more than one therapy for each category.[1]

Clinical implications[1]

This survey highlights considerable differences in the care of patients with MF throughout the UK.[1] Consider the use of prognostic tools to help standardise treatment for patients with MF.

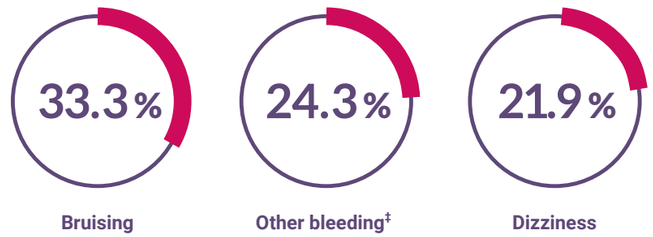
Reference: 1. Harrison CN, et al. Br J Haematol. 2020;188:e80–e112.

JAKAVI® has a well-characterised safety profile[1]

In patients who received JAKAVI® in the COMFORT-I and COMFORT-II trials, the most commonly reported AEs were:*[1]

Haematological AEs†

Non-haematological AEs



Three most frequent non-haematological laboratory abnormalities[1]

40.7% increased alanine aminotransferase
31.5% increased aspartate aminotransferase
25.2% hypertriglyceridaemia

Special warnings and precautions for JAKAVI® include myelosuppression, infections, herpes zoster, progressive multifocal leukoencephalopathy, lipid abnormalities/elevations, MACE, thrombosis, and second primary malignancies.[1] Please refer to the SmPC for full information.

* For full list of AEs, please refer to the SmPC.[1]
† Anaemia, thrombocytopenia and neutropenia are dose-related effects.[1]
‡ Other bleeding included epistaxis, post-procedural haemorrhage and haematuria.[1]

Reference: 1. Novartis Pharmaceuticals NI Ltd. JAKAVI® summary of product characteristics. Last accessed July 2024.

Abbreviations
AE, adverse event; BSH, British Society for Haematology; DIPSS, Dynamic International Prognostic Scoring System; DIPSS+, Dynamic International Prognostic Scoring System Plus; ET, essential thrombocythaemia; HSCT, haematopoietic stem cell transplant; IMID, immunomodulatory drug; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MACE, major adverse cardiac event; MF, myelofibrosis; MIPSS70, Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis; MPN, myeloproliferative neoplasm; MYSEC, Myelofibrosis Secondary; NGS, next-generation sequencing; NICE, National Institute for Health and Care Excellence; PV, polycythaemia vera; PVI, pharmacovigilance intake; QoL, quality of life.

Northern Ireland Prescribing Information: JAKAVI® (ruxolitinib) 5mg, 10mg, 15mg and 20mg tablets. **Important note: Before prescribing, consult Summary of Product Characteristics (SmPC). Presentation**: Tablet (containing lactose). White to almost white tablets with imprints (NVR on one face and L5, L10, L15 or L20 debossed on the other side). **Indications:** Myelofibrosis (MF): Jakavi is indicated for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. Polycythaemia vera (PV): Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea. **Dosage:** *Starting dose*: The recommended starting dose of Jakavi in myelofibrosis is 5 mg twice daily for patients with a platelet count between 50,000/mm^3 and < 75,000/mm^3, 10 mg twice daily for patients with a platelet count between 75,000/mm^3 and < 100,000/mm^3, 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily. *Dose modifications*: Doses may be titrated based on efficacy and safety. If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily. The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals. Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential. Dose reductions should be considered if the platelet count decreases below 100,000/mm^3, with the goal of avoiding dose interruptions for thrombocytopenia. Refer to the full SmPC for details. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl. **Contraindications:** Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Hypersensitivity to the active substance or to any of the excipients listed: cellulose, microcrystalline, magnesium stearate, silica, colloidal anhydrous, sodium starch glycolate (Type A), povidone hydroxypropylcellulose, lactose monohydrate. Pregnancy and lactation. **Warnings and Precautions:** ***Myelosuppression***: Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Treatment should be discontinued in patients with platelet count less than 50,000/mm^3 or absolute neutrophil count less than 500/mm^3. It has been observed that patients with low platelet counts (<200,000/mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi. However, platelet transfusions may be required as clinically indicated. Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10 g/dl. Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered. ***Infections***: Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with Jakavi. Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly. Treatment with Jakavi should not be started until active serious infections have resolved. Tuberculosis has been reported in patients receiving Jakavi. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis has per local recommendations. Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. It is recommended to screen for HBV prior to commencing treatment. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. *Herpes zoster*: Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible. *Progressive multifocal leukoencephalopathy*: Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. *Second primary malignancies*: Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Jakavi. Non-melanoma skin cancers (NMSCs) 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. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. *Lipid abnormalities/elevations*: Treatment with Jakavi has been associated with increases in lipid parameters. Lipid monitoring and treatment of dyslipidaemia according to clinical guidelines is recommended. *Major Adverse Cardiac Events*: Major adverse cardiac events have been reported in patients receiving Jakavi. Prior to initiating or continuing therapy with Jakavi, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older, patients who are current or past longtime smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors. *Thrombosis*: Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Jakavi. Prior to initiating or continuing therapy with Jakavi, the benefits and risks for the individual patient should be considered, particularly in patients with cardiovascular risk factors. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. **Special populations**: *Renal impairment*: No specific dose adjustment is needed in patients with mild or moderate renal impairment. In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment. For patients with end stage renal disease on haemodialysis the starting dose for MF patients should be based on platelet counts. Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy. The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. Please refer to Summary of Product Characteristics for detailed information. *Hepatic impairment*: The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product. *Older people (>65 years)*: No additional dose adjustments are recommended for older people. *Paediatric population*: The safety and efficacy of Jakavi in children aged up to 18 years have not been established. *Withdrawal effects*: Following interruption or discontinuation of Jakavi, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven. **Interaction with other medicinal product** *Strong CYP3A4 inhibitors*: When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2). *Dual CYP2C9 and CYP3A4 inhibitors*: the dose of ruxolitinib should be reduced by 50%. Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily. *Mild or moderate CYP3A4 inhibitors*: No dose adjustment is recommended when Jakavi is co-administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). However, patients should be closely monitored for cytopenias when initiating therapy with a mild/moderate CYP3A4 inhibitor. CYP3A4 inducers: Patients should be closely monitored and the dose titrated based on safety and efficacy. It is possible that in an individual patient, an increase of Jakavi dose is needed when initiating therapy with a strong enzyme inducer. *Cytoreductive therapies*: The concomitant use of cytoreductive therapies with Jakavi was associated with manageable cytopenias. *Oral contraceptives and substances metabolized by CYP3A4*: A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib. **Side-effects:** The most frequently reported adverse drug reactions were thrombocytopenia and anaemia. *Very common*: anaemia, thrombocytopenia, neutropenia, bruising, dizziness, headache, raised alanine aminotransferase, raised aspartate aminotransferase, hypercholesterolaemia, hypertriglyceridaemia, elevated lipase, hypertension, urinary tract infections, pneumonia, herpes zoster, gastrointestinal bleeding, weight gain, constipation and bleeding. *Common*: sepsis, pancytopenia, intracranial bleeding and flatulence. *Uncommon*: Tuberculosis, HBV reactivation. Refer to the SmPC for a full list of all side effects. **Legal Category:** POM. PVC/PCTFE/Aluminium blister packs containing Jakavi 5mg x 56 tablets – MA Number: EU/1/12/773/004-006. Basic NHS price: £1,428; Jakavi 10mg x 56 tablets – MA Number EU/1/12/773/014-016. Basic NHS price: £2,856; Jakavi 15mg x 56 tablets – MA Number: EU/1/12/773/007-009. Basic NHS price: £2,856; Jakavi 20mg x 56 tablets – MA Number: EU/1/12/773/010-012. Basic NHS price: £2,856. Full prescribing information is available on request from Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone (01276) 698370. **Date of revision:** April 2024 UK | 435755-1| May 2024

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report. If you have any questions about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com