NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Fedratinib for splenomegaly and symptoms in myelofibrosis

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of fedratinib within its marketing authorisation for disease related splenomegaly or symptoms from myelofibrosis.

Background

Myelofibrosis is a cancer of the bone marrow in which the marrow is replaced by scar (fibrous) tissue. Myelofibrosis may be primary (known as chronic idiopathic myelofibrosis), or secondary to either polycythaemia vera (a disorder in which the bone marrow makes too many red blood cells) or essential thrombocythaemia (a disorder in which the bone marrow makes too many platelets).

The early stages of myelofibrosis may be asymptomatic in some people while others may have severe symptoms from the onset. As the bone marrow becomes more scarred, it is less able to produce blood cells. To compensate for this, blood cell production occurs in the spleen and liver causing these organs to enlarge. Enlargement of spleen (splenomegaly) may cause abdominal pain, dyspnoea (shortness of breath), early satiety (feeling full) and faecal incontinence, along with progressive anaemia. Splenomegaly can also lead to problems with blood circulation in the liver and spleen. Other symptoms include incurable itch, general malaise, weight loss, night sweats, low grade fever, anaemia, fatigue, and pallor. Between 10 and 20% of people with myelofibrosis develop acute myeloid leukaemia.[1]

Many people with myelofibrosis have mutations in a gene known as Janus-associated kinase 2 (JAK2) gene. JAK signalling controls cytokines and growth factors that are important for blood cell production and immune function. Regardless of mutational status, loss of regulation of the JAK signalling pathway is thought to be the underlying mechanism of the disease in myelofibrosis.

Around 2 to 3 people per 100,000 are diagnosed with myelofibrosis every year.[1] The median survival is 5 years from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival. The peak incidence of primary myelofibrosis is between 50 and 70 years of age.

To guide treatment, myelofibrosis is classified into low, intermediate and high risk categories based on various prognostic factors such as age, presence of constitutional symptoms, haemoglobin level, white blood cell count, platelet

count, circulating blast cells, transfusion dependence, and presence of unfavourable karyotype.

Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, however, it is only suitable for people who are fit enough to undergo treatment. Other treatment options aim to relieve symptoms and improve quality of life. These include hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion.

Ruxolitinib, a protein kinase inhibitor that targets Janus-associated kinase (JAK) signalling, has a marketing authorisation in the UK 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'. NICE technology appraisal guidance 386 recommends ruxolitinib 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.

The technology

Fedratinib (brand name unknown, Celgene) is a small-molecule, adenosine triphosphate (ATP)-competitive inhibitor of Janus-associated kinase 2 (JAK2). It is administered orally.

Fedratinib does not have a marketing authorisation in the UK for treating myelofibrosis. It is currently being studied in a clinical trial compared with placebo in adults with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and intermediate -2 or high-risk disease. It has also been studied in patients previously treated with ruxolitinib and who have symptomatic intermediate -1 risk, intermediate -2 or high risk disease.

Intervention	Fedratinib
Population(s)	Adults with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis
Comparators	• Ruxolitinib (for people with intermediate-2 risk or high risk disease) • Established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion)

Outcomes	The outcome measures to be considered include: • spleen size • symptom relief (including itch, pain and fatigue) • overall survival • progression-free survival • response rate • hematologic parameters (including red blood cell transfusion and blood count) • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows, consideration should be given to the following subgroups according to: • Prior treatment with JAK2 inhibitors • Prognostic factors (haemoglobin <10 g/dL, leukocyte count >25 x 109/L, circulating blasts [immature blood cells] ≥ 1%, presence of constitutional symptoms) or platelet count..
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** 'Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis' (Rev TA289) (2016) NICE technology appraisal guidance 386.

	Review date March 2019. **Appraisals in development (including suspended appraisals)** 'Pacritinib for treating myelofibrosis' NICE technology appraisals guidance [ID880]. Suspended. **Related Cancer Service Guidance:** 'Haematological cancers: improving outcomes' (2016). NICE guideline 47. Review date to be confirmed. **Related NICE Pathways**: Blood and bone marrow cancers, Pathway last updated: September 2016, http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Is the population defined in the scope appropriate?

Have all relevant comparators for fedratinib been included in the scope?

- Is ruxolitinib an appropriate comparator?
- What treatments are currently used in clinical practice to treat adults with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis?

Will fedratinib be used to treat myelofibrosis and/or the symptoms of myelofibrosis?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom fedratinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider fedratinib will fit into the existing NICE pathway, Blood and bone marrow cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which fedratinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider fedratinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of fedratinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 MPN Voice Myelofibrosis. Accessed March 2019. http://www.mpnvoice.org.uk/about-mpns/questions-about-mpns/myelofibrosis.aspx