NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Fedratinib for disease-related splenomegaly or symptoms in myelofibrosis

Final scope

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 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. There is currently no licensed treatment option after ruxolitinib.

The technology

Fedratinib (brand name unknown, Celgene) is a small-molecule, adenosine triphosphate (ATP)-competitive inhibitor of 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 polycythaemia vera myelofibrosis, or post essential thrombocythaemia myelofibrosis and intermediate-2 or high-risk disease. It has also been studied as part of a single-arm study 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 polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis

Comparators	No previous treatment with ruxolitinib • 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) Previous treatment with ruxolitinib or if ruxolitinib is not appropriate • 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

References

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