NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ruxolitinib within its marketing authorisation for treating 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 can be asymptomatic. 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 10-20% of people with myelofibrosis develop acute myeloid leukaemia.

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. Loss of regulation of the JAK signalling pathway is thought to be the underlying mechanism of the disease in the myelofibrosis.

The annual incidence of myelofibrosis is approximately 0.75 per 100,000. 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 is available, through the Cancer Drug Fund, as a first or second line treatment for symptomatic splenomegaly in people with intermediate or high risk primary myelofibrosis, post polycythaemia myelofibrosis, and post essential thrombocytosis myelofibrosis when stem cell transplantation is not suitable. NICE Technology Appraisal Guidance 289 did not recommend ruxolitinib for treating symptomatic splenomegaly in people with myelofibrosis. Additional evidence on the effect of ruxolitinib on longer term survival and disease progression is now available which may help to address some of the key uncertainties identified during the appraisal.

The technology

Ruxolitinib (Jakavi, Novartis) is a protein kinase inhibitor that targets Janus-associated kinase(JAK) signalling. Ruxolitinib is administered orally.

Ruxolitinib has a UK marketing authorisation 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'.

Intervention(s)	Ruxolitinib with established clinical practice
Population(s)	Adults with disease-related splenomegaly or symptoms of • primary myelofibrosis (also known as chronic idiopathic myelofibrosis), • post polycythaemia vera myelofibrosis • post essential thrombocythaemia myelofibrosis
Comparators	Established clinical practice without ruxolitinib
Outcomes	The outcome measures to be considered include: • symptom relief (including itch, pain and fatigue) • overall survival • progression-free survival • changes in spleen size • 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.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows, consideration should be given to subgroups according to prognostic factors (age >65 years, haemoglobin <10 g/dL, leukocyte count >25 x 10^9/L, circulating blasts [immature blood cells] ≥ 1%, presence of constitutional symptoms).
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 289, June 2013, 'Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis' Proposed Technology Appraisal, ID 734, 'Ruxolitinib for treating polycythaemia vera that is resistant or intolerant to hydroxycarbamide'. Earliest anticipated date of publication: TBC Related Cancer Service Guidance: Guidance on Cancer Services, CSGHO, October 2003, 'Improving outcomes in haematological cancers' Related NICE Pathways: NICE Pathway: Blood and bone marrow cancers, Pathway last updated: December 2014, http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	Blood and marrow transplantation services (all ages), Chapter 29, Manual for Prescribed Specialised Services 2013/14 http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1 and 2. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Have all relevant comparators for ruxolitinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for treating myelofibrosis?

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

Where do you consider ruxolitinib 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 ruxolitinib is 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 ruxolitinib 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 ruxolitinib 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.

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)