National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Fedratinib for disease-related splenomegaly or symptoms in myelofibrosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	Celgene Ltd	For the treatment of splenomegaly or symptoms in myelofibrosis. This is in line with the current ruxolitinib NICE Guidance (TA386)	Comment noted, the wording from TA386 has been used.
	MPN Voice	Yes but needs to also take into account that patients who fail a first line JAK inhibitor (usually ruxolitinib) have an extremely poor prognosis	Thank you, your comment has been noted. No changes have been made.
	Novartis Ltd	See below	Noted.
Timing Issues	Celgene Ltd	Currently there is no licensed option other than supportive care for patients who have received ruxolitinib. Life expectancy in these groups of patients is estimated to be less than 2 years, therefore there is an unmet need that Fedratinib could fulfil.	Thank you, your comment has been noted. No changes have been made.
	MPN Voice	Urgent as there are currently no options for patients who fail ruxolitinib therapy (currently the majority)	Thank you, your comment has been noted. No changes have been made.

Section	Consultee/ Commentator	Comments	Action
Additional comments on the draft remit	MPN Voice	Any additional comments on the draft remit: Only that the prevalence figure perhaps only relate to primary not secondary ie PPV or PET MF.	Thank you for your comment. The background section intends to give a brief overview of the disease area. No changes have been made.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Celgene Ltd	The background information does not state that there are currently no licensed options for patients after ruxolitinib.	Thank you for your comment. The background section has been amended.
	MPN Voice	Yes just a comment on prevalence of secondary MF. We think it should also reference how bad the prognosis is for patients who fail ruxolitinib.	Thank you for your comment. The background section intends to give a brief overview of the disease area and treatment options. No changes have been made.
	Novartis Ltd	The WHO diagnostic criteria for MF recognises there are 3 predominant driver mutations which the majority of myelofibrosis patients have- JAK2, MPL and CALR. Allogeneic stem cell transplant is also typically considered earlier for those with higher prognostic risk disease. Ruxolitinib is currently the only licensed JAK inhibitor with 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),	Thank you for your comment. The background section intends to give a brief overview of the disease area and treatment options. No changes have been made.

Section	Consultee/ Commentator	Comments	Action
		post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis' Ruxolitinib is also recommended by the BSH (British society of haematology) 2014 MF treatment guidelines as a first line treatment option for MF patients with symptomatic splenomegaly, MF symptoms impacting QOL and MF related portal hypertension/ hepatomegaly. (Reilly et al_2014 BJH)	
The technology/ intervention	Celgene Ltd	Yes	Noted.
	MPN Voice	Yes.	Noted.
	Novartis Ltd	The description should be more explicit on the nature of the fedratinib clinical trial program. Fedratinib is being studied in a 'phase III placebo controlled clinical trial' in the first line setting. It has also been studied in a 'single-arm, phase II trial' in patients who have previously received ruxolitinib.	Thank you for your comment. The technology section has been updated.
Population	Celgene Ltd	JAKARTA was a phase III, multicenter, randomised, double-blind, placebo-controlled study in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis with splenomegaly, which is covered within the scope. JAKARTA 2 was a phase II, single arm study in adult patients with a current diagnosis of intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis, found to be refractory, relapsed or intolerant to ruxolitinib. Therefore, this population could potentially be considered within the scope	Thank you for your comment. The draft scope takes a broad approach and does not currently specify previous treatment, or risk status. However, to clarify this the comparators section has been split by previous treatment with ruxolitinib.

Section	Consultee/ Commentator	Comments	Action
	MPN Voice	Just we would want to emphasize this drug should be considered in all types of MF and again emphasize second line as well as first line. We note the emphasis on splenomegaly and symptoms but should this not be OR symptoms.	Thank you for your comment. The title and remit have been amended to refer to splenomegaly or symptoms. The committee will only be able to make recommendations for fedratinib within its marketing authorisation. The comparators section has been updated to include previous ruxolitinib treatment.
	Novartis Ltd	The target MF population should be sub divided to reflect the two treatment settings under consideration i.e. first line treatment or in patients who have previously received ruxolitinib (intolerant/refractory).	Thank you for your comment. The draft scope takes a broad approach and does not currently specify previous treatment, or risk status. However, to clarify this the comparators section has been split by previous treatment with ruxolitinib.
	Leukaemia Care	Splenomegaly and other symptoms are outline in the title of the appraisal, but the population defined is just myelofibrosis patients. The population for ruxolitinib was defined more precisely as both splenomegaly and myelofibrosis patients and it would good to have more clarity as to the population of patients that fedratinib is relevant to.	Thank you for your comment. The draft scope takes a broad approach and does not currently specify previous treatment, risk status or splenomegaly. The committee will only be able to make recommendations for fedratinib within its marketing authorisation.
Comparators	Celgene Ltd	Yes	Noted.

Section	Consultee/ Commentator	Comments	Action
	MPN Voice	Yes it can be described as best available care. Also consider ruxolitinib.	Thank you for your comment. The comparators section has been split by previous treatment with ruxolitinib.
	Novartis Ltd	For symptomatic MF patients who are not suitable for ASCT, ruxolitinib is considered standard of care based on the UK BSH treatment guidelines. Ruxolitinib would be the most suitable comparator for fedratinib in this first line setting. In the post-ruxolitinib setting, best available treatment/established clinical practice should be the comparator. The fedratinib phase III clinical trial program does not include any active comparators, only placebo, which does not represent current clinical practice. Any attempt to assess the relative effectiveness of fedratinib versus ruxolitinib in the first line setting would be reliant upon an indirect treatment comparison.	Thank you for your comment. The comparators section has been split by previous treatment with ruxolitinib. The committee will discuss the evidence during the development of the appraisal.
Outcomes	Celgene Ltd	Spleen length could be an additional outcome to be considered.	Thank you, your comment has been noted however spleen length should be included as part of spleen size. No changes have been made.
	MPN Voice	Yes.	Noted.
Economic analysis	Celgene Ltd	As per reference case.	Noted.
	MPN Voice	N/A	Noted.
	Celgene Ltd	None identified.	Noted.

Section	Consultee/ Commentator	Comments	Action
Equality and Diversity	MPN Voice	No issues with equality.	Noted.
Other considerations	Celgene Ltd	None identified	Noted.
	MPN Voice	None.	Noted.
Innovation	Celgene Ltd	Fedratinib selectively inhibits the activity of the JAK2 pathway, thereby representing a potential novel treatment option for patients with myelofibrosis. Fedratinib has a longer half-life than ruxolitinib (67 hours vs 3 hours, respectively), which allows once-daily dosing while maintaining effective concentrations of JAK2 inhibition. The clinical trial programme for fedratinib includes both patients that are JAK inhibitor-naïve and those previously exposed to a JAK inhibitor. The post-JAK inhibitor population has a high degree of unmet need with no licensed treatment options beyond supportive care. Fedratinib, which has a mechanism of action distinct from that of ruxolitinib, has shown efficacy in this patient population.	Thank you, your comments have been noted. The committee will consider the extent to which fedratinib is innovative during the development of the appraisal. No changes have been made.
	MPN Voice	Yes in the same way that ruxolitinib does and if the data for ruxolitinib failure is robust then this technology is a step change. No benefits should be incorporated in the QALY. We understand there were concerns about encephalopathy with this drug this data will need to be provided. We understand there are data from a phase 3 and large phase 2 trial.	Thank you, your comments have been noted. The committee will consider the extent to which fedratinib is innovative during the development of the appraisal. No changes have been made.
	Novartis Ltd	No, fedratinib is not be considered to be innovative; it would potentially be the second licensed JAK-inhibitor class treatment	Thank you, your comments have been noted. The committee will

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		for patients with myelofibrosis. Based on the trial results and design it would appear to be potentially suitable for intermediate 2 or higher severity myelofibrosis patients who are refractory to ruxolitinib. However the definition of ruxolitinib resistance/failure in the fedratinib trials is not well defined- requiring only a minimum of 14 days of prior ruxolitinib treatment and investigator judgement.	consider the extent to which fedratinib is innovative during the development of the appraisal. No changes have been made.
Questions for consultation	Celgene Ltd	As above	Noted.
	Novartis Ltd	Clarification is required on the clinical applicability of the definition of ruxolitinib resistance in the clinical trials (as per comment above)	Thank you, your comments have been noted. The committee will consider the evidence during the development of the appraisal. No changes have been made.
Additional comments on the draft scope	MPN Voice	None	Noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Bristol-Myers Squibb, Department of Health and Social Care