NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for treating polycythaemia vera that is resistant or intolerant to hydroxycarbamide

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Appropriateness	MPN Voice and British Society for Haematology/Royal College of Pathologists	Yes	No changes required
	Novartis Pharmaceuticals UK Limited	Yes	No changes required
Wording	MPN Voice and British Society for Haematology/Royal College of Pathologists	Yes	No changes required
	Novartis Pharmaceuticals UK Limited	Yes	No changes required
Timing Issues	MPN Voice and British Society for Haematology/Royal College of Pathologists	Non-urgent	Comment noted. No changes required
	Novartis Pharmaceuticals	Timing is appropriate	Comment noted. No changes required

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	UK Limited		
Background information	MPN Voice and British Society for Haematology/Royal College of Pathologists	Yes though there is information regarding epidemiology of AML in PV patients from the Swedish Cancer Registry. Data from a French study suggests the rate of AML may be >20% and 25 years and the rate of MF is similar. The rate of thrombosis in this population has not been outlined and is available.	Comment noted. The background provides a brief summary of the condition. No changes required
	Novartis Pharmaceuticals UK Limited	"No epidemiological data are available about the proportion of people receiving treatment for polycythaemia vera whose disease transforms into acute myeloid leukaemia." Novartis disagrees with the above statement. According to Harrison paper, 5 – 10% of polycythaemia vera patients go on to have AML in 10 – 15 years. This should be reflected in the background information.	Comment noted. This has been updated in the scope.
The technology/ intervention	MPN Voice and British Society for Haematology/Royal College of Pathologists	Yes	No changes required
	Novartis Pharmaceuticals UK Limited	Novartis would like to request that the following wording "It has been studied in a clinical trial compared with hydroxycarbamide in adults with polycythaemia vera symptoms despite treatment with a stable dose of hydroxycarbamide for at least 12 weeks prior to entering the study." is removed from the draft scope. It refers to the RELIEF trial, which	Comment noted. The scope has been updated accordingly.

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		comprises a different patient population to that studied in the RESPONSE trial, upon which the marketing authorisation will be based.	
Population	MPN Voice and British Society for Haematology/Royal College of Pathologists	Patients with severe symptoms refractory to standard treatment and patients who are refractory to hydroxycarbamide should be considered.	Comment noted. The patients described are included in the population defined in the scope. No changes required
	Novartis Pharmaceuticals UK Limited	The population is appropriately defined.	Comment noted. No changes required
Comparators	MPN Voice and British Society for Haematology/Royal College of Pathologists	If the hydroxyurea resistant group is considered then all of these therapies should be considered. For patients with refractory symptoms therapies include PUVA etc	Comment noted. Only treatments which are established as standard UK clinical practice will be included in the scope. PUVA is not considered standard UK clinical practice for treating polycythaemia vera. No action required
	Novartis Pharmaceuticals UK Limited	Hydroxycarbamide Although second line use of hydroxycarbamide was high in the RESPONSE trial (it was used in first line for all patients and also in second line in nearly 2/3 of the patients (n = 66; 59%), it does not reflect standard UK clinical practice. Polycythaemia vera patients are generally switched to alternative agents if the disease is uncontrolled on first line cytoreductive therapy. Interferon Novartis requests that “interferon” is replaced with “pegylated interferon” as it is commonly used in UK	Comment noted. At the scoping workshop, clinical experts agreed that hydroxycarbamide was commonly used for polycythaemia vera that is intolerant or resistant to hydroxycarbamide, often in combination with other treatments. Clinical experts attending the scoping workshop indicated that interferon alfa is more commonly used than pegylated interferon, which was not considered to be

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		clinical practice in second line treatment of polycythaemia vera. Immunomodulators Thalidomide and lenalidomide should be included as comparators. These agents were included in RESPONSE trial (4% usage). Phlebotomy Phlebotomy should be included as a comparator as it reflects UK clinical practice. Best supportive care Please see “questions for consultation” section.	established UK clinical practice. No changes required The scoping workshop heard from clinical experts that immunomodulators were not considered established clinical practice in the UK, and therefore these have not been included in the scope. Attendees at the scoping workshop heard from clinical experts that phlebotomy would be used for all patients. The scope has been updated accordingly. .
Outcomes	MPN Voice and British Society for Haematology/Royal College of Pathologists	Prevention of thrombosis is not included and is a major cause of morbidity and mortality for these patients.	Comment noted. Thrombosis has been included as an outcome measure on the scope.
	Novartis Pharmaceuticals UK Limited	Mortality Mortality should be removed as an outcome. It is not the primary clinical goal of treatment in polycythaemia vera. Also, it was not an endpoint in RESPONSE trial. Complete haematological remission Should be included as a separate outcome.	Comment noted. Attendees at the scoping workshop agreed that mortality should remain as an outcome measure to show the benefit ruxolitinib may have on mortality over the lifetime of a patient. Attendees at the scoping workshop agreed that complete haematological remission should

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		Response rate Novartis believes that this outcome should be better defined in the draft scope, as it could potentially include other parameters such as symptom relief and reduction in spleen size.	be included as a comparator in the scope. The scope has been updated accordingly. The attendees at the scoping workshop agreed that response rate should be removed as an outcome measure, as this is already captured under complete haematological remission and symptoms. The scope has been updated accordingly.
Economic analysis	MPN Voice and British Society for Haematology/Royal College of Pathologists	Appropriate	Comment noted. No changes required
Equality	MPN Voice and British Society for Haematology/Royal College of Pathologists	No need to change	Comment noted. No changes required
Innovation	MPN Voice and British Society for Haematology/Royal College of Pathologists	This technology represents a step change to manage symptoms in PV patients Yes many of the symptoms for PV patients such as pruritus which may be extremely severe are not captured. Data from phase 1/2 trial from phase 3 trial. Published data concerning nature and severity of symptoms	Comments noted. The innovative nature of the technology will be considered during the appraisal process. No changes required
	Novartis	If marketing authorisation is granted, ruxolitinib will	Comments noted. The innovative

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	Pharmaceuticals UK Limited	be the first in class targeted agent in polycythaemia vera (PV). Ruxolitinib will be the first agent that exploits the JAK/STAT pathway, which is the pivotal signalling pathway implicated in the pathogenesis of PV. Ruxolitinib will be the first agent that has demonstrated efficacy (significant symptom relief) following hydroxycarbamide resistance/intolerance.	nature of the technology will be considered during the appraisal process. No changes required
Questions for consultation	MPN Voice and British Society for Haematology/Royal College of Pathologists	NA	No changes required
	Novartis Pharmaceuticals UK Limited	How should 'best supportive care' be defined? Novartis considers "watch and wait" to equate to best supportive care. Based on the RESPONSE trial, the "watch and wait" rate was 15%.	Comment noted. The scope has been amended to replace best supportive care with phlebotomy, aspirin and no further treatment.

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

Merck Sharp & Dohme

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation
Summary of comments, action taken, and justification of action:

	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	Add Leukaemia CARE to patient/carer groups.	Leukaemia CARE		Added	Leukaemia CARE requested to be added as a patient/carer group as their interests are closely related to the topic.
2.	Add Leukaemia Cancer Society to patient/carer groups.	NICE Secretariat		Added	Leukaemia Cancer Society's interests are closely related to the topic and as such they have been added as a patient/carer group.
3.	Add Jewish Genetic Disorders UK to patient/carer groups.	NICE Secretariat		Added	Jewish Genetic Disorders UK's interests are closely related to the topic and as such they have been added as a patient/carer group.
4.	Add Thrombosis UK to patient/carer groups.	NICE Secretariat		Added	Thrombosis UK's interests are closely related to the topic and as such they have been added as a patient/carer group.

5.	Add Leukaemia & Lymphoma Research to research groups.	NICE Secretariat		Added	Leukaemia & Lymphoma Research's interests are closely related to the topic and as such they have been added as a research group.
6.	Remove Biogen Idec from comparator manufacturers.	NICE Secretariat		Removed	Biogen Idec no long hold the marketing authorisation for peginterferon alfa-2a and as such have been removed as a comparator manufacturer.
7.	Remove Health Research Authority from research groups.	NICE Secretariat		Removed	The Health Research Authority no longer wish to be consulted regarding NICE Technology Appraisals and as such have been removed as a research group.