NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA386; Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis

Original publication date:	23 March 2016
Review date	March 2019
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA386, see Appendix A.

1. Proposal

We propose to that TA386 is transferred to the 'static guidance list.'

2. Rationale

We did not identify any new evidence that would change the existing recommendation in TA386. The recommendation is optimised for a narrower population than covered by the marketing authorisation. We found no new RCT evidence that would change the existing recommendation or would warrant reassessment for the full marketing authorisation.

The company has confirmed that no changes in the marketing authorisation are anticipated and is not aware of any new evidence that would change the existing recommendations.

It is therefore considered appropriate to move TA386 to the static list.

3. Summary of new evidence and implications for review

TA386 assessed the use of ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis. The committee made an optimised recommendation for people with intermediate-2 or high-risk disease. Ruxolitinib is not recommended for people with intermediate-1 disease because there was a lack of RCT evidence.

We identified follow-on publications for the RCTs that were included in TA386. These RCTs included people with intermediate-2 or high-risk disease. The new publications present longer-term, up to 5 years, efficacy and safety data. The results presented in the recent publications broadly support the conclusions in TA386 and are unlikely to change the recommendations.

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We did not identify RCTs that included people with intermediate-1 disease.

We identified 1 RCT that compares the efficacy and safety of momelotinib with ruxolitinib. The results show non-inferiority of momelotinib for some endpoints but not others. It is unlikely that these results would change the existing recommendation.

Has there been any change to the price of the technology(ies) since the guidance was published?
The company reduced the list price of ruxolitinib by around 20% since the publication of TA386. The company confirmed that there are no changes to the PAS prices.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no proposed changes to the marketing authorisation that would affect the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
TA386 recommends the use of ruxolitinib in a narrower population than that covered in the Marketing Authorisation. TA386 recommends treatment with ruxolitinib only in people with intermediate-2 or high-risk disease. The company provided RCT evidence in this population and restricted their health-economics analysis to this population. There were no outstanding uncertainties identified in TA386 for this population. Since publication of TA386 in 2013 the company published long-term, up to 5 years, efficacy and safety data. These data support the recommendation published in TA386. The recommendation in TA386 does not cover people with intermediate-1 disease. This population is covered in the Marketing Authorisation. The company did not provide RCT evidence or health-economics analysis for this population for assessment in TA386. Since publication of TA386 there is no new evidence for this population.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
Not applicable.

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from 9th December 2014 to 29th January 2019 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature

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search are discussed in the ‘Summary of evidence and implications for review’ section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues were identified during the development of TA386.

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of ruxolitinib within its marketing authorisation for treating myelofibrosis

6. Current guidance

1.1 Ruxolitinib is recommended 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, and
- if the company provides ruxolitinib with the discount agreed in the patient access scheme.

1.2 People whose treatment with ruxolitinib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

Not applicable

8. Cost information from original guidance

£3,360 for a 56‑tablet pack of 10 mg, 15 mg or 20 mg tablets, or £1,680 for a 56‑tablet pack of 5 mg tablets (British national formulary [BNF], December 2015).

The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ruxolitinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

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Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific trial or date.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

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Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

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Appendix C – other relevant

1. Relevant Institute work

Published

None

In progress

Fedratinib for splenomegaly and symptoms in myelofibrosis. NICE technology appraisal guidance. Publication date to be confirmed

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Indication: *"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".* **Price:** The list price at the time of TA386 was £3,360 for a 56-tablet pack of 10 mg, 15 mg or 20 mg tablets, or £1,680 for a 56-tablet pack of 5 mg tablets (British national formulary [BNF], December 2015). The company agreed a patient access scheme which provides a simple discount to the list price of ruxolitinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.	**Indication:** No change **Price:** £2,856.00 for a 56-tablet pack of 10 mg, 15 mg or 20 mg tablets, or £1,428.00 for a 56-tablet pack of 5 mg tablets (BNF online, accessed 5th February 2019)

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3. Registered and unpublished trials

Trial name and registration number	Details
CINC424A2X01B Rollover Protocol NCT02386800; 2014-003527-22; CINC424A2X01B	5 year, single arm, open label follow-up to previous ruxolitinib trials. Measured outcomes are safety rather than efficacy-focused. n = 96 Ongoing Completion date estimated Q3 2020

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Appendix D – References

Anonymous (2017) Erratum: long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis (Leukemia (2016) 30 (1701-1707) DOI: 10.1038/leu.2016.148). Leukemia 31(3): 775

Harrison, C. N., Vannucchi, A. M., Kiladjian, J. J. et al. (2016) Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia 30(8): 1701-7

Mesa, Ruben A., Kiladjian, Jean-Jacques, Catalano, John V. et al. (2017) SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naive Patients With Myelofibrosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 35(34): 3844-3850

Verstovsek, S., Gotlib, J., Mesa, R. A. et al. (2017) Long-Term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and-II pooled analyses. Journal of Hematology and Oncology 10(1): 527

Verstovsek, Srdan, Mesa, Ruben A., Gotlib, Jason et al. (2017) Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. Journal of hematology & oncology 10(1): 55

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