Evidence Review Group Report

Ruxolitinib for the treatment of myelofibrosis

Erratum

Amended paragraphs

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Whilst the evidence from the two good quality RCTs demonstrates that ruxolitinib is more effective than BAT and placebo at achieving a ≥35% reduction in spleen volume, the ERG believes the use of this outcome may generate an optimistic response rate. The manufacturer has provided evidence from a Phase I/II study that this endpoint equates to the spleen reduction criterion for 'clinical improvement' according to the IWG-MRT consensus criteria for treatment response in myelofibrosis (≥50% reduction in palpable spleen length for patients with a palpable spleen that is at least 10 cm at baseline); however, in the opinion of the ERG there is some uncertainty about the equivalence of MRI assessment and palpation assessment, and the application of the ≥35% cut-off across all baseline spleen sizes may be inappropriate.[a]

The other criteria for demonstrating 'clinical improvement', defined by the IWG-MRT consensus criteria for treatment response in myelofibrosis, relate to reductions in the haematological symptoms of MF. Importantly, ruxolitinib does not have a favourable effect on haematological symptoms such as anaemia and thrombocytopenia; these are in fact worsened at least in the short term[b] by treatment in some patients and were assessed only in terms of their being adverse events. In addition, treatment response was not assessed against complete remission or partial remission criteria defined by the IWG-MRT.

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The effect of ruxolitinib on MF symptoms was assessed in the placebo controlled COMFORT-I trial using the modified Myelofibrosis Symptom Assessment Form (MFSAF) version 2 and the Patient's Global Impression of Change (PGIC) instrument. In COMFORT-II the EORTC-QLQ C30 was used to assess some MF-related symptoms.[c]

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The analyses undertaken by the ERG included:

- survival assumptions
    - ICER ranged from £74,274 to £79,303
- definition of response criteria
    - ICER ranged from £79,536 to £90,557
- discontinuation rates
    - ICER ranged from £74,616 to £88,622

[a] Amended further to manufacturer's Factual Error Check report
[b] "at least in the short term" added further to manufacturer's Factual Error Check report
[c] Amended further to manufacturer's Factual Error Check report

- utility values
    - ICER ranged from £97,105 to £109,092[d]
- resource use and cost
    - ICER ranged from £75,141 to £80,874

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The model presented in the MS does not fully capture disease progression. In addition to the structural issues, some of the underlying modelling assumptions may be considered by some to be clinically implausible.[e]

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The description of the aetiology, epidemiology and treatment of MF is generally adequate. However, whilst the debilitating symptoms of MF and their effects on quality of life are summarised correctly, the impression given is that all symptoms are secondary to splenomegaly.[f]

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The mortality risk of patients with MF is detailed appropriately in the MS. The MS usefully summarises the various prognostic scoring systems. The BCSH guidelines indicate that the DIPSS Plus is the most relevant to clinical practice, but in the trials of ruxolitinib the IPSS is used (Table 2.1). The MS does not provide any information on the distribution of the different risk groups in the UK. It should also be noted that the product licence for ruxolitinib is not framed in terms of these levels of risk: all levels of risk are covered by the product licence provided patients have splenomegaly or symptoms. However, as stated earlier the BCSH guidelines suggest that ruxolitinib is suitable for patients with profound constitutional symptoms, which are usually associated with massive splenomegaly and elevated levels of proinflammatory cytokines.[g]

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Through the MS the status of three therapies used in the management of MF[h] is unclear: blood transfusions, splenectomy and splenic irradiation. None of these therapies is clearly described nor is any treated as comparators of ruxilitinib or included as a component of BAT. In the economic model splenectomy and splenic irradiation, and to a lesser extent, transfusions are incorporated as complications of MF, with only the disutilities or costs of treatment included, whilst any benefits are not.

[d] Corrected for the value copied over from Table 6.11 page 118 to Section 1
[e] Amended further to manufacturer's Factual Error Check report

[f] Amended further to manufacturer's Factual Error Check report
[g] "and elevated levels of proinflammatory cytokines" added further to manufacturer's Factual Error Check report
[h] Amended further to manufacturer's Factual Error Check report

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It should be noted that, although the stated population matches the NICE scope, the evidence presented in the MS is derived from clinical trials whose populations represent only a subset of the licensed population (see Section 4.2.1). However, whilst the licence is very broad, it is likely that in clinical practice patients treated with ruxolitinib will be those recommended in the BCSH guidelines,[3] i.e. patients with profound constitutional symptoms, which are usually associated with massive splenomegaly and elevated levels of proinflammatory cytokines.[i]

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The outcome measures specified in the NICE scope were very general: symptom relief (including pain and fatigue); overall survival; progression-free survival; response rate; changes in body weight; adverse effects of treatment; and HRQoL. The manufacturer modified these to more closely reflect the clinical trials (and effects) of ruxolitinib. Most notably spleen size reduction (as a measure of response rate) is the first outcome stated in the MS decision problem. Other outcomes addressed were impact on symptom burden, overall survival, progression-free survival, changes in body weight, AEs and HRQoL. Progression-free survival was defined in the COMFORT-II CSR as the interval between randomization and the occurrence of any one of these events: a spleen volume increase (25% or greater increase in spleen volume from the on-study nadir (including baseline); leukaemic transformation; splenic irradiation; splenectomy; or death. This definition was not included in the MS.[j]

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There were no inclusion criteria related to symptoms of MF. Figure 4.1 displays participants' baseline symptom scores for the COMFORT-I trial assessed using the modified MFSAF version 2 (this is Figure 14 of the MS). The mean TSS at baseline was 18.0 for ruxolitinib-treated patients and 16.5 for placebo-treated patients (out of a potential maximum score of 60 indicating worst possible symptoms). Baseline symptom scores for the COMFORT-II trial were not reported in the MS as TSS was not assessed[k], however 69% patients in the ruxolitinib group and 63% patients in the BAT group had constitutional symptoms at baseline, including weight loss, fever and night sweats. Therefore, fewer participants in the COMFORT-II trial appear to have had constitutional symptoms at baseline, than in the COMFORT-I trial (80.5% ruxolitinib patients and 83.6% placebo patients had night sweats at baseline, as displayed in Figure 4.1).

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The COMFORT-II trial compared ruxolitinib with best available therapy (BAT), including observation alone (33% patients), antineoplastic agents (hydroxyurea and anagrelide; 51% patients), glucocorticoids (prednisone/prednisolone and methyprednisolone; 16% patients), anti-anaemia preparations (epoetin-alpha), immunomodulatory agents (thalidomide and lenalidomide), purine analogs (mercaptopurine and thioguanine), antigonadotropins and similar (danazol), interferons (PEG-interferon-alpha 2a and interferon-alpha), nitrogen

[i] "and elevated levels of proinflammatory cytokines" added further to manufacturer's Factual Error Check report
[j] Definition of progression-free survival added further to manufacturer's Factual Error Check report
[k] Amended further to manufacturer's Factual Error Check report

mustard analogs (melphalan) and pyrimidine analogs (cytarabine).[22] These comparators were generally appropriate, although lenalidomide is very rarely[l] used in UK practice.[15]

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A 35% reduction in spleen volume for those patients with a smaller spleen at baseline may have little impact on patients' symptoms or HRQoL (although patients may still see improved symptoms or HRQoL).[m] For this reason, the emphasis on a 35% or more reduction in spleen volume as the primary outcome, above symptom relief, overall survival and HRQoL, does not appear to be appropriate.

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Survival

Neither of the COMFORT trials were designed to be sufficiently powered to detect a significant difference in survival outcomes. The COMFORT-II trial assessed overall survival, progression-free survival and leukaemia-free survival. Progression-free survival was defined in the COMFORT-II CSR as the interval between randomization and the occurrence of any one of these events: a spleen volume increase (25% or greater increase in spleen volume from the on-study nadir (including baseline); leukaemic transformation; splenic irradiation; splenectomy; or death.[n] The COMFORT-I trial assessed overall survival.

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A 50% reduction in palpable spleen length (which the manufacturer claims corresponds to a 35% reduction in spleen volume, based on data from 24 patients in the phase I/II trial[o]) is one of the criteria for demonstrating clinical improvement in the IWG-MRT consensus criteria for treatment response in myelofibrosis, however, this is for patients with a spleen at least 10 cm at baseline; a spleen that is more than 5 cm at baseline should become non-palpable for a clinical improvement to have been achieved. Therefore, some patients with a baseline palpable spleen length of less than 10 cm may not have met the IWG-MRT criteria for clinical improvement.

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The manufacturer undertook a systematic review of cost-effectiveness studies including ruxolitinib. Based on their findings they developed a de novo economic decision model. The model presented is a state-transition Markov model, comprising four mutually exclusive health states, which reflect the treatment of MF (responder, non-responder, discontinuation and death). The time horizon for the base case was 35 years. The model uses a spleen volume reduction of ≥35%[p] as the response criterion.

[l] Corrected from "not very rarely" further to manufacturer's Factual Error Check report
[m] "(although patients may still see improved symptoms or HRQoL)" added further to manufacturer's Factual Error Check report
[n] Definition of progression-free survival added further to manufacturer's Factual Error Check report
[o] "based on data from 24 patients in the phase I/II trial" added further to manufacturer's Factual Error Check report
[p] "35%" corrected to "≥35%" further to the manufacturer's Factual Error Check report

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Base case results were presented as an incremental cost-effectiveness ratio (ICER) for ruxolitinib compared with BAT. The results showed that ruxolitinib has an ICER of £73,980 per QALY compared with BAT. Sensitivity analysis conducted by the manufacturer generally produced ICERs for ruxolitinib compared to BAT that were similar to or higher than the base case ICER.[q] The full range of sensitivity analysis conducted by the manufacturer will be presented in Section 5.2.9, Sensitivity analyses.

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A summary of treatment included in BAT in the COMFORT-II trial is presented in Table 5.3. It is not clear from the data in what order the treatments were received, how long patients remain on each treatment, nor how many treatments each patient might receive. Information the ERG found from the CSR for COMFORT-II indicates that 33.9% of patients in the trial received no active treatment; whilst this is likely to have been accounted for in the model the ERG were not able to validate the data.[r]

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The ERG believes that these simplifications make the result of the modelling presented in the MS highly uncertain.[s]

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The MS states that overall survival data from the COMFORT trials was not mature enough, insufficiently powered, plagued by missing values, and too confounded by crossover to be able to demonstrate any mortality benefits between ruxolitinib and the comparator treatment groups (BAT or placebo). However, the ERG requested updated survival data from the COMFORT trials in the points for clarification document and the manufacturer was able to provide the updated survival data from both the COMFORT-I and II trials which were published as abstracts on 5 November (which was after the initial appraisal submission date).[t] These data will be used by the ERG to undertake an alternative analysis which will be presented in Section 6.

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The MS applied the same probability of death at each 12 week cycle for all non-responders, regardless of whether the non-responder had initially receive ruxolitinib as a treatment or BAT; this was justified by the manufacturer on the basis that ruxolitinib patients who were non-responders moved to the BAT arm after just 24 weeks (see Table 5.5). The ERG feels that until more mature survival data are reported it is unclear whether this assumption is conservative or not. On one hand, patients who are treated with ruxolitinib and who continue

[q] Amended further to manufacturer's Factual Error Check report
[r] Amended further to manufacturer's Factual Error Check report
[s] Amended further to manufacturer's Factual Error Check report

[t] Amended further to manufacturer's Factual Error Check report

to respond for several years before having their treatment stopped might actually achieve a slightly better survival compared with patients who never achieve a response with ruxolitinib, or whose duration of treatment response is short/shorter. On the other hand, patients treated with ruxolitinib have a higher risk of AEs (compared to BAT) and this risk of AEs and their associated treatment might increase with treatment duration.[u] In light of the lack of evidence the assumption made in the MS is reasonable.

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Table 5.11 Utility values used in the de-novo model (MS, Table B22, pg. 161)

Health state	Model base case	SA (CML)	SA (NHL)
Baseline (all patients start in the non-responder state)	0.446 (Eribulin appraisal) [1]	0.595 (Imatinib)[42]	0.62 (Rituximab appraisal) [43]
Responders	0.823 [1]	0.854 (Imatinib appraisal)[42]	0.88 (Rituximab appraisal) [43]
Non-responders	0.446 (Eribulin appraisal) [1]	0.595[v] (Imatinib appraisal)[42]	0.62 (Rituximab appraisal) [43]
Complications of MF	decrement in utility of 10% manufacturer's assumption	decrement in utility of 10%, manufacturer's assumption	decrement in utility of 10% manufacturer's assumption

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As currently constructed, the model assumes no drug wastage. This assumption may not accurately reflect drug usage in practice. The ERG has some concern about drug wastage considering that the shelf-life of the drug after the bottle of medication opened[w] is only 30 days.[9] Given that most AEs are managed by dose reduction or interruption it is possible that drugs would expire before all were used, leading to additional costs. There is no evidence to support what sort of impact drug expiry might have on overall costs.

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When transfusion dependence was added to the model, the ICER for ruxolitinib increased to £75,887 (MS, Section 7.7.7, Table B39, pg. 196). When an additional state for LT was added the ICER increased to £79,184 (MS, Section 7.7.7, Table B38, pg. 196). The manufacturer states that approximately 20% of MF patients die due to LT, therefore, it is appropriate for the costs entailed in LT to be included in the evaluation of cost-effectiveness. It was also shown that patients taking ruxolitinib were more likely to become transfusion dependent than BAT patients (COMFORT-II CSR, pp. 124-5) in the short-term, however there is some uncertainty regarding the rates in the longer-term.x

[u] Amended further to manufacturer's Factual Error Check report
[v] Amended further to manufacturer's Factual Error Check report
[w] Amended further to manufacturer's Factual Error Check report, to make clear 30 days is after bottle opened
[x] Amended further to manufacturer's Factual Error Check report

Table 5.17 Testing if the results from the manufacturer's model behave as expected[y]

Per-patient outcomes: lifetime	Ruxolitinib	BAT	difference
Months as a Responder	16.90	18.71	-1.80
Number of Splenectomies	0.00	0.00	0.00
Number of Splenic Irradiation	0.00	0.00	0.00
Number of Other Complications	0.00	0.00	0.00
Overall Survival (months)	47.85	47.85	0.00
Leukemia-free Survival (months)	47.85	47.85	0.00
Quality-Adjusted Life-Years	3.99	3.99	0.00

[y] Amended further to manufacturer's Factual Error Check report