NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Ruxolitinib is not recommended within its marketing authorisation, that is, 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.

1.2 People currently receiving ruxolitinib should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Ruxolitinib (Jakavi, Novartis) 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'. Ruxolitinib is a protein kinase inhibitor that targets Janus-associated kinase 2 (JAK2) signalling. It is administered orally. The recommended starting dose is 15 mg twice daily for patients with a platelet count
between 100,000/mm$^3$ and 200,000/mm$^3$, and 20 mg twice daily for patients with a platelet count of more than 200,000/mm$^3$.

2.2 The summary of product characteristics lists the following adverse reactions for ruxolitinib: anaemia, thrombocytopenia, neutropenia, bleeding and weight gain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of ruxolitinib is £3600 for a 60-tablet pack of 15 mg or 20 mg tablets, or £1800 for a 60-tablet pack of 5 mg tablets (excluding VAT; British National Formulary [BNF] online, November 2012). This corresponds to an annual cost of approximately £43,200 per patient (assuming a 15 mg or 20 mg dose, taken twice daily, 30 days per month). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer’s submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of ruxolitinib and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer submitted evidence on the clinical and cost effectiveness of ruxolitinib compared with best available therapy. The manufacturer presented data from 3 clinical trials: 2 randomised controlled trials (COMFORT-I and COMFORT-II) and 1 dose-finding non-randomised trial (NCT00509899). The clinical trials investigated ruxolitinib in patients with primary myelofibrosis, or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.
Clinical effectiveness

Background to the clinical evidence

3.2 COMFORT-I was a multicentre (USA, Canada and Australia), phase III, randomised, double-blind trial that compared ruxolitinib (15 mg or 20 mg twice daily, n=155) with placebo (n=154) in patients with primary myelofibrosis (45.2% of ruxolitinib arm; 54.5% of placebo arm), or myelofibrosis secondary to polycythaemia vera (32.3% of ruxolitinib arm; 30.5% of placebo arm) or essential thrombocythaemia (22.6% of ruxolitinib arm; 14.3% of placebo arm). Patients enrolled in the trial had resistant or refractory myelofibrosis, or available therapy was contraindicated or not tolerated. All patients on the trial had intermediate-2 risk or high-risk myelofibrosis (defined using the International Prognostic Scoring System [IPSS]), and a palpable spleen length of at least 5 cm. Exclusion criteria included an absolute neutrophil count of $1 \times 10^9$/litre or less, and a platelet count of less than $100 \times 10^9$/litre. The duration of the study was 24 weeks. All analyses presented in the manufacturer’s submission used the intention-to-treat population.

3.3 COMFORT-II was a multicentre (Europe, including sites in the UK), phase III, randomised, open-label trial that compared ruxolitinib (15 mg or 20 mg twice daily, n=146) with best available therapy (n=73) in patients with primary myelofibrosis (53% of ruxolitinib arm; 53% of placebo arm), or myelofibrosis secondary to polycythaemia vera (33% of ruxolitinib arm; 27% of placebo arm) or essential thrombocythaemia (14% of ruxolitinib arm; 19% of placebo arm). Best available therapy comprised a range of treatments. The most frequently used were hydroxycarbamide, prednisone and epoetin alfa. Other treatments used as best available therapy included lenalidomide and thalidomide. All
patients in the trial had intermediate-2 risk or high-risk myelofibrosis and a palpable spleen length of at least 5 cm. Other inclusion criteria included a platelet count of at least $100 \times 10^9$/litre and an absolute neutrophil count of at least $1 \times 10^9$/litre. Exclusion criteria included a history of absolute neutrophil counts of $0.5 \times 10^9$/litre or less, or a history of platelet counts of less than $50 \times 10^9$/litre, except during treatment for myeloproliferative neoplasm or cytotoxic therapy. The duration of the core study was 48 weeks, after which patients could enter an open-label extension phase. All analyses presented in the manufacturer’s submission used the intention-to-treat population.

3.4 NCT00509899 was a phase I/II open-label, non-randomised study (n=153) that investigated ruxolitinib doses in patients with primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia at 2 centres in the USA (the MD Anderson cancer centre [MDACC] and the Mayo clinic). The following dosages of ruxolitinib were investigated: 10 mg twice daily (n=29), 15 mg twice daily (n=35), 25 mg twice daily (n=47), 50 mg twice daily (n=5), 25 mg once daily (n=6), 50 mg once daily (n=22), 100 mg once daily (n=6) and 200 mg once daily (n=3). Inclusion criteria included patients with intermediate-1, intermediate-2 or high-risk myelofibrosis. There were no inclusion criteria relating to spleen size. Follow-up analysis was provided for the whole population at a median of 14.7 months. Further analyses were conducted at each centre separately, after a median of 32 months at the MDACC, and a median of 42 months at the Mayo clinic. As the study was single-arm, data analysis used historical control groups.

3.5 The primary outcome for both COMFORT-I and COMFORT-II was the proportion of patients having a spleen volume reduction of 35%
or more from baseline, assessed by MRI or CT scan. Spleen volume was measured at a range of time points. The primary efficacy outcome was measured at 24 weeks in COMFORT-I and 48 weeks in COMFORT-II. Secondary outcomes for the COMFORT-I trial included maintenance of reduction in spleen volume, reduction in palpable spleen length, change in total symptom score (measured using the modified myelofibrosis symptom assessment form v2.0 diary), overall survival and health-related quality of life. Secondary outcomes for COMFORT-II were the same as those in COMFORT-I, but also included time to a spleen volume reduction of 35% or more, progression-free survival, leukaemia-free survival and transfusion dependency.

3.6 The primary outcomes of NCT00509899 included adverse events, treatment-emergent adverse events and clinical improvement over time (defined according to the International Working Group for Myelofibrosis Research and Treatment [IWG-MRT] criteria). Secondary outcomes included the efficacy outcomes of change in spleen volume and length, change in total symptom score (as measured by the modified myelofibrosis symptom assessment form v2.0 diary), and health-related quality-of-life.

Spleen size results

3.7 For the primary outcome of COMFORT-I, the results presented by the manufacturer showed a statistically significant increase in the proportion of patients who had a greater than 35% decrease in spleen volume with ruxolitinib compared with placebo (42% compared with 1%, p<0.001) after 24 weeks. Many patients who had received ruxolitinib (39%) had this response by week 12. The mean percentage change in spleen volume and palpable spleen length from baseline were maintained over 48 weeks.
3.8 Similar results were presented by the manufacturer for COMFORT-II. A statistically significantly larger proportion of patients had a reduction in spleen volume of 35% or more with ruxolitinib than with best available therapy (28% compared with 0%, \( p<0.001 \)) after the primary end point of 48 weeks. As observed in COMFORT-I, the response was rapid: 64% of the 69 ruxolitinib-treated patients who had a greater than 35% reduction in spleen volume did so by week 12. The median time to response in the ruxolitinib group was 12.3 weeks. The mean percentage decrease in spleen volume from baseline was maintained over 60 weeks in the ruxolitinib arm, but the mean percentage change in spleen volume increased in the best available therapy group.

**Symptom results**

3.9 The manufacturer presented symptom scores from COMFORT-I. Total symptom score was measured using the modified myelofibrosis symptom assessment form, and a reduction of 50% or more was used as a measure of response. Statistically significantly more patients had a 50% or more reduction in total symptom score with ruxolitinib (45.9%) than with placebo (5.3%) at week 24 (\( p<0.001 \)). Additionally, a significantly greater reduction in mean percentage change from baseline total symptom score was observed in patients treated with ruxolitinib (−46.1%) than with placebo (+41.8%) at week 24 (\( p<0.001 \)). The total symptom score response was rapid, and most patients whose symptom scores improved had a 50% or more reduction after 4 weeks.

**Survival results**

3.10 The manufacturer presented data from COMFORT-I that showed, at a median follow-up of 51 weeks, a survival advantage for patients who received ruxolitinib compared with placebo (hazard ratio [HR] 0.5; 95% confidence interval [CI] 0.25 to 0.98; \( p=0.04 \)).
There were 13 deaths in the ruxolitinib arm (8.4%) and 24 deaths in the placebo arm (15.7%). This advantage was observed despite the fact that patients could cross over from the placebo to the ruxolitinib arm after 24 weeks, and the analysis assumed no crossover. At the time point for data analysis, almost all patients in the placebo group had crossed over to receive ruxolitinib (n=111, 72.1%; median time to switching was 41.1 weeks), or had discontinued the study (n=38, 24.7%).

3.11 The manufacturer reported in its submission that statistically significant differences in overall survival, progression-free survival and leukaemia-free survival were not observed between the ruxolitinib and best available therapy treatment arms of COMFORT-II. The manufacturer noted that any survival benefit was likely to be underestimated because of the crossover observed (at 61 weeks, at the time of the second overall survival analysis, approximately 25% of patients who had received best available therapy had crossed over to receive ruxolitinib).

3.12 The manufacturer presented results of the NCT00509899 dose-finding trial that showed a significant survival difference between patients who received ruxolitinib and historical controls (HR 0.58, p=0.005). After the initial report of this study (median follow-up of 14.7 months), the patients at the MDACC (n=107) and the Mayo clinic (n=51) were studied separately. Analysis at the MDACC after a median of 32 months showed that 30.8% of ruxolitinib patients had died compared with 60.9% of historical controls (310 historical control patients were identified from 3 large databases and matched on the basis of study inclusion criteria). This was statistically significant for the high-risk (IPSS) subgroup (HR 0.50, p=0.006) but not for patients with intermediate-2 risk. The manufacturer stated that no survival benefit with ruxolitinib was
observed in the group who were studied at the Mayo clinic after a median of 42 months compared with a historical control cohort consisting of 410 patients with primary myelofibrosis who were treated with standard therapy at the Mayo clinic in the previous 10 years.

Health-related quality-of-life results

3.13 The manufacturer presented health-related quality-of-life data from COMFORT-I and COMFORT-II, measured using the European Organisation for Research and Treatment of Cancer's quality-of-life questionnaire (EORTC QLQ-C30). The EORTC QLQ-C30 is a non-preference based, cancer-specific quality-of-life instrument. The global health status and quality of life of patients who received ruxolitinib in COMFORT-I improved after 24 weeks with a mean change of +12.3, whereas for patients who received placebo, it worsened with a mean change of −3.4; these responses were statistically significantly different (p<0.001). A similar result was observed in COMFORT-II, with an improvement of +9.1 in the ruxolitinib arm, and +3.4 with best available therapy after 48 weeks.

3.14 The manufacturer also described health-related quality-of-life data measured using the functional assessment of cancer therapy-lymphoma (FACT-Lym) score in COMFORT-II. FACT-Lym is a cancer specific, non-preference based instrument for measuring quality of life. After 48 weeks, the mean change from baseline in the ruxolitinib arm was +11.3 (representing an improvement in health-related quality of life), and in the best available therapy arm it was −0.9 (representing worsening of health-related quality of life).

Subgroup analyses

3.15 The manufacturer described a pre-planned subgroup analysis of COMFORT-I that showed no statistically significant difference
between the types of myelofibrosis (primary or secondary to polycythaemia vera or essential thrombocythaemia) responding to ruxolitinib treatment (in terms of the proportion of patients who had a 35% or greater reduction in spleen volume, mean change in spleen volume, or mean change in total symptom score). Post-hoc subgroup analysis comparing response to ruxolitinib (in terms of mean change in spleen volume and mean change in total symptom score) in patients with or without grade 3 or 4 anaemia showed no statistically significant difference.

3.16 The manufacturer presented a pre-planned subgroup analysis of the COMFORT-II trial data that showed there was no significant difference in the proportion of patients who had a 35% or greater reduction in spleen volume with ruxolitinib across subgroups defined according to sex, myelofibrosis subtype and IPSS risk category. Post-hoc analysis also showed no statistically significant difference in the proportion of patients with or without the JAK2 mutation having a 35% or greater reduction in spleen volume.

Adverse effects of treatment

3.17 The data presented by the manufacturer demonstrated that all 3 trials show that ruxolitinib is generally well tolerated in patients who have primary myelofibrosis or myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia. The incidence of adverse events was similar, with or without ruxolitinib, in both COMFORT trials. The most frequently occurring grade 3 or 4 adverse events with ruxolitinib, across all studies, were anaemia and thrombocytopenia, which generally decreased with continued ruxolitinib treatment, and were managed with dose adjustments. Transfusions were sometimes needed to manage haematological adverse events, and in the COMFORT trials these were more frequently observed with ruxolitinib than with best available therapy.
or placebo. In COMFORT-II, 51% of patients treated with ruxolitinib needed at least 1 blood transfusion, compared with 38% of those treated with best available therapy. Grade 3 or 4 non-haematological adverse events were infrequent in COMFORT-I and COMFORT-II, and were generally more common in the placebo or best available therapy groups than with ruxolitinib.

**Cost effectiveness**

3.18 The cost-effectiveness evidence presented by the manufacturer consisted of a systematic literature review and a de novo model. In addition, in response to the appraisal consultation document (ACD) consultation, the manufacturer provided revised cost-effectiveness analyses. A literature review was conducted to identify all existing studies of cost effectiveness of any intervention in patients with myelofibrosis, but did not identify any relevant studies.

**Model overview**

3.19 The manufacturer’s model was a state-transition Markov model designed to simulate the natural course of myelofibrosis. The model used a 12-week cycle and a 35-year time horizon. Costs and benefits were both discounted at 3.5%. The manufacturer’s model consisted of 4 mutually exclusive health states: ‘responder’, ‘non-responder’, ‘discontinuation’ and ‘death’. Patients enter the model at diagnosis of myelofibrosis with splenomegaly, and progress through the model according to spleen volume response. On receiving treatment with best available therapy or ruxolitinib, patients can move to the responder health state (defined as at least 35% reduction in spleen volume) or the non-responder health state (defined as less than 35% reduction in spleen volume). Patients in the non-responder health state can develop complications, whereas those in the responder health state cannot. The model includes a stopping rule at 24 weeks, up to which point the model
assumes patients are treated for 24 weeks with ruxolitinib or best available therapy, irrespective of response. During the initial 24 weeks, patients can move to the discontinuation health state, but cannot progress to the death state. After 24 weeks, the model assumes patients are evaluated and those who have a 35% or more reduction in spleen volume continue on treatment in the responder health state (until death or discontinuation), and those who do not move to best available therapy in the non-responder health state (until death).

3.20 The manufacturer used response rates in the model that were estimated using data from COMFORT-II. The survival estimates used in the model for the responder health state were derived from the MDACC in the NCT00509899 trial. Survival estimates for the non-responder health state were taken from the literature. The rate of complications observed in the non-responder health state was estimated using expert opinion and data from a US chart review and the Haematological Malignancy Research Network database. Transfusion dependence and transformation to leukaemia (leukaemic transformation) were not included in the base case of the model. However, sensitivity analyses were conducted by the manufacturer that included these. COMFORT-II data were used to inform the rate of transfusion dependence, and it was assumed that a 50% rate would apply to both ruxolitinib and best available therapy. Leukaemic transformation rates were assumed to be 3.6% for the responder health state and 3.8% for the non-responder health state, based on the literature and data from the MDACC in the NCT00509899 trial.

3.21 To estimate the cost of ruxolitinib in the manufacturer’s model, a dosage of between 10 mg and 20 mg twice daily was assumed and the associated list price was applied. The cost estimate for best
available therapy in the manufacturer’s model was based on the proportion of patients and the average dose observed for each treatment in COMFORT-II. The associated cost for each treatment was taken from the BNF (edition 62). In addition to treatment costs, the costs of GP visits, outpatient attendance and overnight stays in hospital were estimated for patients in the non-responder health state from a Haematological Malignancy Research Network audit and using assumptions if data were not available. NHS reference costs were used to estimate the cost of splenectomy, splenic irradiation, transfusions, complications and adverse events. The resource costs associated with the responder health state were assumed to be 30% of those identified for the non-responder health state.

3.22 The EORTC QLQ-C30 quality-of-life data measured in the trials were not used to derive utilities for the base case of the model; instead the manufacturer considered it appropriate to use the utility values reported in Eribulin for the treatment of locally advanced or metastatic breast cancer (NICE technology appraisal guidance 250): responder health state, 0.823; non-responder health state, 0.446. The breast cancer utility values were considered appropriate because a study comparing the EORTC QLQ-C30 data in COMFORT-II with data from trials in commonly known cancers concluded that compared with all cancer patients of similar age, patients with myelofibrosis had similar or worse global health status or quality of life, functioning and symptom burden. Utility values associated with chronic myeloid leukaemia (responder health state, 0.854; non-responder health state, 0.595) and non-Hodgkin’s lymphoma (responder health state, 0.880; non-responder health state, 0.620) were used in sensitivity analyses.
Base-case results and sensitivity analyses

3.23 The base-case ICER estimated in the manufacturer’s model was £73,980 per quality-adjusted life year (QALY) gained (based on £85,027 incremental cost and 1.15 incremental QALYs). A univariate sensitivity analysis was conducted and the most sensitive parameters driving the ICER were found to be the discount rates for outcomes and costs (0–6%, in line with the Guide to the methods of technology appraisal), the utility value of the responder health state, the survival benefit with ruxolitinib and the cost of best available therapy.

3.24 The manufacturer presented sensitivity analyses, which included using different utility values, applying leukaemic transformation and including transfusion dependence in the model. The estimated ICERs per QALY gained were £77,092 using chronic myeloid leukaemia utility values (incremental cost £85,027, incremental QALYs 1.10), £75,123 using non-Hodgkin’s lymphoma utility values (incremental cost £85,027, incremental QALYs 1.13), £79,184 including leukaemic transformation (incremental cost £72,080, incremental QALYs 0.91) and £75,887 including transfusion independence (incremental cost £87,219, incremental QALYs 1.15). In addition, when the manufacturer shortened the time horizon of the model from 35 years in the base case to 10 or 15 years, the corresponding ICERs were £81,308 and £77,036 per QALY gained respectively.

3.25 The manufacturer conducted a scenario analysis that compared ruxolitinib with specific best available therapies, as recommended for splenomegaly and constitutional symptoms in the 2012 British Committee for Standards in Haematology guidelines. The guidelines recommend hydroxycarbamide for patients who have splenomegaly, and thalidomide plus prednisolone or lenalidomide.
for patients who cannot take hydroxycarbamide. The clinical efficacy for hydroxycarbamide was calculated from COMFORT-II. It was assumed that the efficacy of thalidomide plus prednisolone or lenalidomide was the same as best available therapy (as observed in COMFORT-II). It was also assumed that half the patients would take lenalidomide and the other half would take thalidomide plus prednisolone. Comparison of ruxolitinib with hydroxycarbamide gave an ICER of £76,584 per QALY gained (based on an incremental cost of £88,020 and incremental QALYs of 1.15), whereas comparison with thalidomide plus prednisolone or lenalidomide gave an ICER of £48,275 per QALY gained (based on an incremental cost of £55,483 and incremental QALYs of 1.15).

3.26 A second base-case scenario was also considered by the manufacturer, whereby the threshold for response was lowered to a 25% or more reduction in spleen volume, and the stopping rule was reduced to 12 weeks. The base-case ICER was £66,453 per QALY gained (based on an incremental cost of £120,411 and incremental QALYs of 1.81). Similar to the 35% threshold analysis, a one-way sensitivity analysis showed that the ICER was most sensitive to the discount rates for outcomes and costs (0–6%), the utility value of the responder and non-responder health states, survival benefit with ruxolitinib, and the cost of best available therapy. The manufacturer presented sensitivity analyses, which included using different utility values, applying leukaemic transformation and including transfusion dependence in the model. The estimated ICERs per QALY gained were £69,227 using chronic myeloid leukaemia utility values (incremental cost £120,411, incremental QALYs 1.74), £67,457 using non-Hodgkin’s lymphoma utility values (incremental cost £120,411, incremental QALYs 1.78), £69,682 including leukaemic transformation (incremental cost £100,116, incremental QALYs 1.44) and £68,311 including transfusion.
independence (incremental cost £123,776, incremental QALYs 1.81). When the manufacturer adopted shorter time horizons for the model base-case of 10 or 15 years, the corresponding ICERs were £71,183 and £68,511 per QALY gained respectively.

3.27 The probabilistic sensitivity analysis conducted by the manufacturer found that there was a 0% probability of ruxolitinib being cost effective at £30,000 per QALY gained.

**Evidence Review Group comments**

**Clinical effectiveness**

3.28 The ERG commented that the search strategy used by the manufacturer was appropriate, comprehensive and well documented. No relevant studies of ruxolitinib were overlooked and all 3 studies presented to the European Medicines Agency were included.

**Critique of the clinical trials**

3.29 The ERG commented that COMFORT-I and COMFORT-II were directly relevant to the decision problem and that COMFORT-I compared ruxolitinib with placebo, and therefore reflected the decision problem if ruxolitinib was end-of-line therapy. The ERG noted that COMFORT-I and COMFORT-II only included patients who had intermediate-2 risk or high-risk myelofibrosis, and that patients were excluded from the trial if they had an absolute neutrophil count of $1 \times 10^9$/litre or less, a platelet count less than $100 \times 10^9$/litre or if they were eligible for haematopoietic stem cell transplant. The population represented in the trial was therefore narrower than that covered by the marketing authorisation. The manufacturer had commented that because the efficacy of ruxolitinib is based on spleen size rather than risk group, the
efficacy of ruxolitinib would be expected to be comparable across the different risk groups, and therefore should be generalisable to the population in the marketing authorisation (which includes all risk groups).

3.30 The ERG noted that the population in NCT00509899 was more applicable to the marketing authorisation than the population in the final NICE scope, because it included patients with intermediate-1 risk myelofibrosis (who have a better prognosis) and there was no need to have a palpable spleen of at least 5 cm (that is, splenomegaly).

3.31 It was noted by the ERG that the proportion of patients with the different subtypes of myelofibrosis in the COMFORT trials did not reflect the global prevalence data reported by the manufacturer. Primary myelofibrosis was reported to be around 30 times more common than post-polycythaemia myelofibrosis and post-essential thrombocythaemia myelofibrosis, but in the trials, patients with primary myelofibrosis made up around only 50% of the population. The ERG noted that although a statistically significant difference in response between different types of myelofibrosis was not observed in the COMFORT trials, the data suggested possible differential effects. The ERG stated that this may warrant further exploration in adequately powered clinical trials.

3.32 The ERG noted that the COMFORT trials were not powered to measure overall survival or to detect statistically significant differences between subgroups (for example according to sex, myelofibrosis subtype, IPSS risk category or JAK2 mutation status).

3.33 It was noted by the ERG that, for some outcomes from the COMFORT trials (actual change in spleen volume, actual change in symptoms, global health status and global quality of life), there
were missing patient data, unaccounted for by the manufacturer. The ERG stated that this questions the reliability of the available results, and how representative they are of the whole trial population.

**Critique of the comparator ‘best available therapy’**

3.34 COMFORT-II used best available therapy as its comparator arm, which the ERG considered appropriate. However, the ERG also noted that the mode of action of the comparator therapies and the symptoms they target is varied; few comparator treatments would be expected to have an effect on spleen size, with many targeting the haematological symptoms of myelofibrosis, such as leukocytosis, thrombocytosis, cytopenias and anaemia. After reviewing trials associated with these therapies, the ERG noted that different therapies affect different aspects of myelofibrosis and therefore should be assessed using different outcome measures. The ERG felt that to determine the efficacy of ruxolitinib, or any comparators, all aspects of myelofibrosis, including haematological events, should be considered as well as spleen size.

**Critique of measure of response**

3.35 The ERG critiqued the use of a 35% or more reduction in spleen volume as the primary outcome of the COMFORT trials. The ERG recognised that a reduction in spleen volume, measured using MRI, is an objective measure. However, an assessment of spleen length by palpitation is considered by the ERG to be more clinically relevant because this is how spleen size is assessed in clinical practice. The manufacturer stated that a 35% or more reduction in spleen volume was equivalent to a 50% or more reduction in palpable spleen length, which is one of the criteria for demonstrating clinical improvement defined by IWG-MRT. The ERG noted that this is not a generally accepted assumption, but is
based on data from the NCT00509899 dose-finding study. Therefore, the ERG's opinion was that the emphasis on a 35% or more reduction in spleen volume as the primary outcome, above symptom relief, overall survival and quality of life, did not appear to be appropriate.

3.36 The ERG requested further information from the manufacturer about using a 50% reduction in total symptom score as a definition of symptom response. The ERG noted that the results presented suggested that there is a reasonable correlation between a 50% or more reduction in the total symptom score and meaningful benefit reported by patients (in terms of ‘Patients’ global impression of change’ scores), but there was uncertainty around this: some patients whose condition responded, did not report improvements; and some patients whose condition did not respond, did report improvements. In addition, it was noted that much of the data were missing for the placebo patients, which undermines the reliability of the results.

Critique of haematological adverse events

3.37 The ERG confirmed that haematological adverse events were very common with ruxolitinib, particularly thrombocytopenia and anaemia. It also commented that anaemia is a common symptom associated with myelofibrosis, and whereas some treatments specifically target haematological symptoms of myelofibrosis, ruxolitinib exacerbates these symptoms in some patients, at least in the short term. COMFORT-I indicated that ruxolitinib-treated patients with new-onset grade 3 or 4 anaemia experienced improvements in spleen volume and symptoms that were similar to those in ruxolitinib-treated patients without anaemia. No data were presented about thrombocytopenia from COMFORT-II.
Critique of overall survival data

3.38 The ERG considered the COMFORT-II data to be the most relevant and reliable in terms of estimating overall survival. This is because it included a relevant comparator group, with fewer control group patients having crossed over to ruxolitinib or discontinued than in COMFORT-I (see sections 3.10 and 3.11). The ERG commented that there were small numbers of patients at the later time points, which made the data difficult to interpret. The ERG stated that the NCT00509899 survival data cannot be considered appropriate because the doses of ruxolitinib used in this trial do not reflect the licensed dose, and long-term survival data are presented separately for the 2 centres in the trial, meaning few patients were included in the analyses (see section 3.12). The ERG commented that there was no improvement in progression-free survival with ruxolitinib.

Cost effectiveness

3.39 The ERG considered the systematic literature review for economic evaluations conducted by the manufacturer to be appropriate and comprehensive. The ERG considered the structure of the manufacturer’s model, and stated that although a Markov model is appropriate for chronic progressive conditions, in this instance the progression of myelofibrosis had been oversimplified and disease progression had not been captured. As a result, the ERG considered the model structure to be inappropriate to fully address the decision problem.

3.40 The ERG stated that some of the basic underlying assumptions of the model may be too limiting, making the results of the model unreliable. These include the following:
• The inability of the responder and non-responder health states to capture disease progression.

• People in the responder health state maintaining the same level of spleen volume reduction observed at week 24 and the associated utility benefits (that is, outcomes are constant over time), unless they discontinue treatment.

• Overall survival, discontinuation rates and complication rates are assumed to be constant over time after the initial treatment phase (24 weeks).

• Only people in the non-responder health state are at risk of the complications of myelofibrosis. However, some of these complications may not be decreased by a reduction in spleen size.

• People in the non-responder health state who survive remain on best available therapy for the duration of the model (base case 35 years).

3.41 The ERG noted that complications were only assigned to the non-responder health state. The manufacturer justified this assumption by stating that all complications are because of splenomegaly. The ERG commented that this is not entirely accurate because infection and sepsis are related to blood cell count, which is independent of splenomegaly. In addition, it is likely that splenectomy and splenic irradiation are treatment options for progressed splenomegaly, not complications of the condition. Therefore the ERG suggested that splenectomy and splenic irradiation should be included as separate health states in the model, rather than being included as complications, because the complications health state of the manufacturer’s model is only applicable to the non-responder health state and response is determined by spleen size only. The ERG stated that the model does not fully capture the impact of these treatments in terms of costs and outcomes.
3.42 The ERG recognised that using a 35-year time horizon in the base case meets the NICE reference case. However, the ERG considered that the time horizon could be too long because the median survival stated in the submission is 5 years for patients with intermediate-2 risk and high-risk myelofibrosis. The manufacturer presented some additional analyses using shorter time horizons (10 and 15 years), which increased the ICER. Currently no long-term data are available but the ERG stated that it may be unrealistic to suppose that if patients survive, they will continue on treatment (ruxolitinib or best available therapy) and gain a treatment response or benefit for 35 years.

3.43 The ERG commented on the survival estimates used in the model for the responder and non-responder health states. For the non-responder health state, the ERG noted that estimates were based on the Cervantes et al. study. It stated that it was not clear whether the survival data from this study were relevant to the current UK best available therapy because the population did not include patients with secondary myelofibrosis, and the study was conducted between 1980 and 2007. The ERG also noted that the manufacturer’s submission assumed an exponential distribution for extrapolating survival. The manufacturer clarified that other survival distributions had not been explored but indicated that the results of the sensitivity analysis showed that survival had little impact on the ICER. For the responder health state, the ERG noted that the manufacturer’s model assumed identical hazard ratios for high-risk and intermediate-2 risk groups and that survival data from other sources, such as the COMFORT trials, were not explored.

3.44 The ERG noted that the discontinuation rates applied to the responder health state were derived from the NCT00509899 study. The use of these rates rather than those from the COMFORT trials
was not justified by the manufacturer. The long-term follow-up data from the COMFORT trials indicated higher discontinuation rates for ruxolitinib than in NCT00509899. Given that COMFORT-II informed the primary efficacy inputs used in the model, the ERG stated that discontinuation rates from COMFORT-II may have been more appropriate, and at a minimum should have been considered in the sensitivity analysis.

3.45 The ERG considered the ‘best available therapy’ used in the model, and commented that the order, duration and dose of each treatment were unclear. However, to estimate cost, it was assumed within the model that patients received the full 12 weeks of treatment. The manufacturer stated that the British Committee for Standards in Haematology guidelines reinforce that all current treatments are only temporarily effective for managing myelofibrosis and symptoms (including splenomegaly). In light of this, the ERG considered it inappropriate that patients in the non-responder health state are considered to take active best available therapy until death because this potentially overestimates the cost of best available therapy treatment. In addition, the inclusion of lenalidomide was considered inappropriate by the ERG clinical specialist because it is not routinely prescribed in the UK. The ERG also noted that the cost of lenalidomide had a high impact on the best available therapy cost. The ERG calculated that if the cost of lenalidomide is omitted from the best available therapy, the overall cost of best available therapy falls from £702.03 to £402.03, and if lenalidomide is replaced with hydroxycarbamide the cost falls to £402.65.

3.46 The ERG considered the utility values used within the manufacturer’s model. The utility values used were from metastatic breast cancer utility data, and alternative utility values were
explored in sensitivity analysis using chronic myeloid leukaemia and non-Hodgkin’s lymphoma utility data. The ERG stated that there is a high level of uncertainty surrounding the appropriateness of the utility estimates assumed to represent myelofibrosis.

3.47 The ERG reviewed the sensitivity analysis conducted by the manufacturer, and concluded that it was unclear whether the use of +/-20% was sufficient variance to represent uncertainty surrounding a number of the parameters. The ERG stated that there is a high level of uncertainty surrounding survival, utilities and cost of best available therapy. The results of the one-way sensitivity analysis showed that varying these has a significant impact on the ICER, mostly leading to an increased ICER.

3.48 The manufacturer presented an analysis comparing ruxolitinib with hydroxycarbamide, and an analysis comparing ruxolitinib with thalidomide or lenalidomide. The ERG considered the results of both these analyses irrelevant. This was because hydroxycarbamide is the most commonly used treatment in myelofibrosis, but it is by no means the only one. In addition, the ERG considered the scenario in which lenalidomide is evaluated to be inappropriate because the ERG’s clinical specialist and the Haematological Malignancy Research Network audit indicated that lenalidomide is rarely used to treat myelofibrosis in the UK.

ERG exploratory analysis

3.49 The ERG conducted an exploratory analysis to address some of the important areas of uncertainty. Each ERG analysis was completed with or without leukaemic transformation. The manufacturer did not include leukaemic transformation in the base case of the model, but included a leukaemic transformation health state in the model to conduct sensitivity analysis. The probabilities
of leukaemic transformation used in the manufacturer’s model differed between ruxolitinib (3.6%) and best available therapy (3.8%). The ERG stated that excluding leukaemic transformation from the base case was not justified. In addition, the ERG clinical specialist indicated that the conservative assumption would be equivalent rates between ruxolitinib and best available therapy. For the exploratory analysis conducted by the ERG, leukaemic transformation rates were assumed to be equal between ruxolitinib and best available therapy (3.6%). Most of the analyses resulted in an increase in the ICER. The largest increases were observed when the utility values used in the model were mapped from COMFORT-II (£109,092 per QALY gained, incremental cost £85,027, incremental QALYs 0.76 [non-responder health state, 0.670; responder health state, 0.754]), when survival inputs were estimated from the COMFORT trials (£90,557 [COMFORT-I] and £88,278 [COMFORT-II] per QALY gained), and when discontinuation rates from COMFORT-II were applied (£88,622 per QALY gained).

3.50 The ERG conducted a scenario analysis using alternative assumptions to combine several of the uncertainties used in the model at the same time. The changes to the base case were as follows:

- Reduced the time horizon to 15 years.
- Leukaemic transformation was included with equivalent rates.
- Transfusion dependence was allowed (included within the manufacturer’s sensitivity analysis).
- Utilities mapped from the EORTC QLQ-C30 questionnaire data were collected in COMFORT-II.
- Survival hazard ratios were used from long-term COMFORT-II data.
When these were combined, the resulting ICER was £148,867 per QALY gained. The ERG recognised that these data may be no more certain than the manufacturer’s data, but stated that they are as plausible as those presented in the base case. In addition, the ERG commented that if disease progression had been included, then it is likely the ICER would increase further.

3.51 The ERG concluded that the model presented by the manufacturer does not fully capture disease progression. In addition to the structural issues, some of the underlying modelling assumptions were considered not to be clinically plausible. The additional analyses undertaken by the ERG showed that most of the plausible modifications to the model inputs resulted in an increase in the ICER. The ERG stated that the lack of disease progression captured in the model and the lack of long-term data make obtaining a more robust estimate of the ICER difficult. It is, however, likely that the base-case ICER presented by the manufacturer represents a best-case scenario.

**Additional evidence, including manufacturer’s revised economic analyses, submitted in response to ACD consultation**

3.52 Alongside their ACD comments, the manufacturer requested permission to submit additional evidence and a revised economic analysis. This was approved by NICE and considered by the Committee. The manufacturer provided updated survival hazard ratios, a dose intensity adjustment, additional utility values and estimates of carer costs in response to the ACD consultation. The updated survival hazard ratios provided were for the responder group. These were estimated at 48 weeks using follow-up data from COMFORT-II. The hazard ratio was estimated for those
patients who received ruxolitinib and had at least a 35% reduction in spleen volume. A dose intensity adjustment estimate (commercial-in-confidence) was provided by the manufacturer for its revised economic analyses. The manufacturer stated that a dose intensity adjustment should be applied because dose interruptions and reductions would mean that in clinical practice a lower dose would be used. The additional utility values provided by the manufacturer were derived from an Australian study, which used the standard gamble technique with the general public to estimate myelofibrosis-specific utilities. The utility values were similar to those for breast cancer but are academic-in-confidence.

3.53 The manufacturer included carer costs in its revised economic analyses. The manufacturer stated that these costs were added because the results of a study had shown that up to 18% of people with myelofibrosis have a medical disability. In addition, a survey of clinicians indicated that up to 25% of people with myelofibrosis could receive formal care. Carer costs were extracted from the Personal Social Services Research Unit, and related to 4 activities of daily living: using the stairs, getting around outside, dressing and bathing. These costs were £327 per week for the entire population. For the revised economic analysis base case this was applied to 18% of the non-responder health state. Carer costs were also determined for the high-risk patients and were incorporated into a high-risk group scenario. The high-risk carer costs included another 3 activities of daily living: using the toilet, getting around inside and transferring between chair and bed. These were assumed to be £847 per week, and were applied to 25% of the non-responder health state for the high-risk group scenario.

3.54 The manufacturer provided a revised base case presented by the manufacturer included transfusion dependence, a 15-year time
horizon, Australian utility values (see section 5.52), survival hazard ratios estimated from patients who received ruxolitinib and had at least a 35% reduction in spleen volume on COMFORT II (see section 5.52), carer costs (£327 per week for 18% of the non-responders health state) (see section 5.53), and a dose-intensity adjustment (see section 5.52). The subsequent ICER was £56,963 per QALY gained (incremental cost £77,437, incremental QALYs 1.36).

3.55 The manufacturer conducted 2 sensitivity analyses of the revised model base case. Firstly, carer costs were added to the responder health state. These costs were 30% of the costs applied to the non-responder health state. This increased the ICER to £58,548 per QALY gained (incremental cost £79,592, incremental QALYs 1.36). Secondly, leukaemic transformation was included in the model. This increased the ICER to £59,281 per QALY gained (incremental cost £66,031, incremental QALYs 1.11).

3.56 The manufacturer submitted an analysis for patients with high-risk myelofibrosis. The revised model inputs were used (see section 3.54). However, the carer costs amounted to £847 per week, and were applied to 25% of the non-responder health state (see section 3.53). The resulting ICER was £55,175 per QALY gained (incremental cost £61,327, incremental QALYs 1.11). The manufacturer conducted 2 sensitivity analyses of the high-risk base case. Firstly, carer costs were added to the responder health state, at 30% of the costs applied to the non-responder health state. This increased the ICER to £59,839 per QALY gained (incremental cost £66,510, incremental QALYs 1.11). Secondly, leukaemic transformation was included in model, which increased the ICER to £57,117 per QALY gained (incremental cost £52,411, incremental QALYs 0.92).
**ERG critique of the additional evidence, including manufacturer’s revised economic analyses, submitted in response to ACD consultation**

3.57 The ERG reviewed the survival estimates used in the manufacturer’s revised economic analyses. The ERG noted that these estimates were based on patients who were still alive at 48 weeks in the best available therapy arm, and those who were still alive and had at least a 35% reduction in spleen volume in the ruxolitinib arm. The ERG commented that this was likely to favour ruxolitinib as only those patients with a long-term response would be included. The ERG stated that new hazard ratios reduced the 12-week probability of death from 1.12% to 0.4% (intermediate-2) and from 2.13% to 0.71% (high-risk). The ERG noted that the hazard ratio was still assumed to remain constant over time. To understand the impact on the ICER, the ERG applied the new hazard ratios to the original model submitted by the manufacturer. This reduced the ICER from £78,694 per QALY gained (incremental cost £80,700, incremental QALYs 1.03) in the base case to £72,768 per QALY gained (incremental cost £99,075, incremental QALYs 1.36) with the new hazard ratios.

3.58 The ERG commented on the Australian utility values included in the revised economic analysis. The ERG noted that the study was conducted using a general population sample rather than a myelofibrosis or ruxolitinib patient population. The ERG stated that these utility values were no more certain than those derived from the mapping exercise of COMFORT II data to the EQ-5D, and that the new analysis did not reduce the uncertainty surrounding the utility values assigned.
3.59 The ERG reviewed the use of a dose-intensity estimate. The ERG commented that the previous assumption of 10 mg to 20 mg per day was reasonable. The ERG noted that dosing adjustments would not necessarily lead to cost savings because doses of 10 mg and 20 mg twice daily incurred the same cost. The ERG recognised that some savings may be made through titration, dose adjustment and interruptions but it is unclear whether the adjustment is appropriate and would be realised in clinical practice. The ERG conducted an analysis of the revised base case, without the dose intensity adjustment. This resulted in an ICER of £71,294 per QALY gained (incremental cost £96,920, incremental QALYs 1.36), which showed that this adjustment may be key in reducing the revised base-case ICER.

3.60 The ERG commented on the use of disability care costs. The ERG reviewed the study by Mesa et al., and noted that it did not include patients receiving ruxolitinib, medical disability was not clearly defined, it did not capture the risk category of the patients, and did not link the medical disability to what (if any) formal care was needed. The ERG also reviewed the clinician survey, and commented that it was unclear who, or how many people, undertook the survey, and that the survey did not capture the risk category of the patient nor the type and number of hours of care needed. The ERG also noted that the impact of ruxolitinib treatment on disability was not reported. In addition, the ERGs clinical advisor commented that the proportion of patients stated by the manufacturer to receive care (18% of the whole population, 25% of high-risk patients), was likely to be higher than that observed in clinical practice.

3.61 The ERG reviewed the model structure in terms of modelling of disease progression, the 15-year time horizon and the exclusion of
leukaemic transformation. The ERG maintained that a health state could have been included for ‘loss of spleen response’ to capture disease progression. The ERG noted that the model holds much of the data derived at 24 weeks constant over the duration of the model (including utilities, survival and response rates). However, relevant data (at 24 and 48 weeks) indicated that response rates were not constant over time. The ERG stated that given the severity of the condition, constant response rates over a prolonged period of time were unlikely. Therefore the chronic, progressive nature of the disease is likely to have been underestimated by the model. The ERG commented on the use of a 15-year time horizon and clarified that a shorter time horizon can mitigate the impact of constant rates over time. However, had time-dependant rates and appropriate distributions been used, using a 15-year time horizon would not have been preferable. In addition, the ERG confirmed its view that leukaemic transformation should be included in the model.

3.62 Full details of all the evidence are in the manufacturer’s submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ruxolitinib, having considered evidence on the nature of splenomegaly in people with myelofibrosis and the value placed on the benefits of ruxolitinib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
4.2 The Committee considered the treatment pathway and the position of ruxolitinib within it. The Committee heard from clinical specialists that the management of patients with myelofibrosis and splenomegaly or symptoms varies and that patients change treatment regularly. The Committee understood from the clinical specialists that none of the treatments available affect the underlying disease process but are used to manage the different symptoms that present, such as those due to anaemia. The Committee noted that the **British Committee for Standards in Haematology guidelines** recommend managing splenomegaly and constitutional symptoms with hydroxycarbamide as first-line treatment, and lenalidomide or thalidomide as second-line treatment. The Committee heard from the clinical specialists that patients who are intolerant to hydroxycarbamide would discontinue this treatment but the next treatment would not always be lenalidomide or thalidomide. The clinical specialists also explained that thalidomide is used but lenalidomide is rarely used. The Committee concluded that there were no targeted treatments available to manage splenomegaly and associated symptoms, and therefore ruxolitinib would be positioned as a first-line treatment for these patients.

4.3 The Committee considered the generalisability of the clinical trials for ruxolitinib to the UK population covered by the marketing authorisation. It noted that the COMFORT trials included only patients who had intermediate-2 risk or high-risk myelofibrosis, but that the marketing authorisation was not defined by risk categories. The Committee heard from clinical specialists that ruxolitinib would mostly be used in higher-risk patients who had splenomegaly and/or symptoms. The Committee noted that the proportion of patients with primary or secondary myelofibrosis in the trial was not representative of the UK population covered by the marketing
authorisation (see sections 3.2, 3.3 and 3.32). The clinical specialists highlighted that there was no difference in the management or outcome between primary and secondary myelofibrosis in clinical practice. The Committee concluded that the trial populations were generalisable to the patients who would be treated with ruxolitinib in UK clinical practice; that is, those with intermediate-2 or high-risk myelofibrosis.

4.4 The Committee considered the impact of splenomegaly and myelofibrosis on patients’ wellbeing. It heard from patient experts and clinical specialists how debilitating myelofibrosis can be and that one of the most problematic and untreatable symptoms was extreme itch. The clinical specialists commented that extreme itch was a prevalent symptom leading to despair and depression. Additionally, the patient experts described being fatigued to the point of choosing to lie down rather than sit up just to conserve energy and the need for afternoon naps. The patient experts explained that the fatigue did not directly correlate to anaemia and haemoglobin levels and that greater fatigue could be experienced with improved red blood cell counts. The impact of these symptoms on quality of life was further supported by comments received in response to the ACD consultation. The Committee concluded that improving the symptoms associated with myelofibrosis, particularly the itch, would be beneficial to the wellbeing of patients with myelofibrosis.

Clinical effectiveness

4.5 The Committee discussed the clinical-effectiveness evidence for ruxolitinib and acknowledged that the clinical trials presented were directly relevant to the decision problem. The Committee considered the impact of ruxolitinib on spleen size. It noted from the results of COMFORT-I and -II that statistically significantly more
patients treated with ruxolitinib had at least a 35% reduction in spleen volume compared with best available therapy or placebo. The Committee therefore concluded that ruxolitinib was effective in reducing spleen size.

4.6 The Committee considered the use of ‘greater than 35% spleen volume reduction’ as a measure of response. The Committee recognised the ERG’s comments that the trials had measured spleen volume by MRI, a method that is not routinely used in UK clinical practice to evaluate spleen response. However, it was also aware of comments from clinical specialists that MRI offers a more robust measure than the routinely used spleen palpation (which is subjective) and it is a relevant and valid outcome for clinical trials. The clinical specialists explained that because MRI is an expensive technique it would not be used in clinical practice and ultrasound would be more commonly used. The Committee concluded that spleen volume measured using MRI was a valid outcome for clinical trials.

4.7 The Committee considered the relationship between spleen size and symptoms. It heard from clinical specialists that there was no direct association between spleen size and symptoms and that a patient could have a modest-sized spleen with severe symptoms or a large spleen with minimal symptoms. The patient experts commented that a much enlarged spleen was not necessarily limiting in day-to-day activities. However, the clinical specialists stated that it was better for a patient to have a smaller spleen than a larger one because they were less likely to develop problems. The Committee noted that the results from COMFORT-I indicated a trend between reductions in spleen volume and improvements in modified myelofibrosis symptom assessment form diary scores. The Committee was aware of the emphasis that patient experts
placed on symptoms in myelofibrosis (see section 4.4), and concluded that symptoms (especially itch and fatigue) and spleen size were both important outcomes.

4.8 The Committee discussed the impact of ruxolitinib on haematological outcomes (for example anaemia and thrombocytopenia). The Committee heard from the clinical specialists that haematological outcomes are important in the management of myelofibrosis. However, the Committee noted that in the COMFORT trials haematological outcomes had only been considered in the context of adverse events. The Committee noted the results from the COMFORT trials that ruxolitinib had a negative impact on haematological outcomes, leading to dose reductions and an increase in transfusions (see section 3.18). However, the Committee heard from the clinical specialists that recent conference data (American Society of Haematology, December 2012), not included in the manufacturer’s submission, had shown that the initial negative impact on haematological outcomes with ruxolitinib stabilised over time. The clinical specialists also commented that ruxolitinib dose reductions rather than transfusions were the main means of treating haematological problems. It was noted by the Committee that this analysis was from trials that had excluded patients with poor blood cell counts (see sections 3.2 and 3.3). The Committee concluded that ruxolitinib did have a negative impact on haematological outcomes in the short term, but agreed that these were manageable.

4.9 The Committee considered the impact of ruxolitinib on other symptoms. The Committee heard from patient experts that ruxolitinib resolved both itch and fatigue. The clinical specialists agreed that ruxolitinib was associated with symptom relief. The Committee noted that in COMFORT-I significantly more patients
treated with ruxolitinib had a 50% or more reduction in total symptom score than those on placebo, and that there was a significantly greater reduction in mean change from baseline total symptom score with ruxolitinib than placebo. The Committee was aware that no evidence had been presented on changes in symptom score for patients in COMFORT-II. On balance, the Committee concluded that ruxolitinib reduced symptoms such as itch and fatigue, which are associated with myelofibrosis and splenomegaly.

4.10 The Committee discussed the overall survival data. The Committee noted that an overall survival benefit was observed in COMFORT-I (compared with placebo) and at 1 of the 2 centres of the NCT00509899 trial, the MDACC, but was not observed in COMFORT-II (compared with best available therapy) or at the Mayo clinic centre in the NCT00509899 trial. The Committee heard from the manufacturer that an update to the COMFORT-II data analysis (2-year follow-up) did not show a statistically significant survival benefit with ruxolitinib. However, the Committee recognised that those whose spleen did respond to ruxolitinib (had an at least 35% reduction in spleen volume) did show a significant survival benefit, compared with those receiving best available therapy. The Committee acknowledged that the impact of ruxolitinib on myelofibrosis progression remained unknown. The Committee understood from clinical specialists that although splenomegaly should not be considered a proxy for survival, it is associated with both morbidity and mortality. The Committee concluded that it was plausible that ruxolitinib could offer a survival benefit. However, the reason for this benefit remained unclear.

4.11 The Committee discussed the appropriateness of the IWG-MRT criteria for clinical improvement as a measure of response. The
Committee noted that ruxolitinib improved only 1 of 4 IWG-MRT criteria (palpable splenomegaly). The clinical specialists explained that the IWG-MRT criteria were primarily used to assess eligibility for transplant and were rarely used in clinical practice. The Committee concluded that considering the impact of ruxolitinib on symptoms and spleen size was just as relevant as meeting the IWG-MRT criteria.

**Cost effectiveness**

4.12 The Committee considered the available cost-effectiveness evidence. It discussed the manufacturer’s analyses and the base-case ICER of £74,000 per QALY gained from the original submission and £57,000 per QALY gained in the revised economic analysis for ruxolitinib compared with best available therapy. The Committee noted the ERG’s concerns around the model structure and related assumptions (see section 3.41) including the maintenance of response, survival and discontinuation rates over time, no disease progression, no complications for patients in the responder health state, and continuation of best available therapy throughout the time horizon. The Committee recognised that including loss of response in the model would be feasible and considered it to be important to capture the progressive nature of myelofibrosis. The Committee understood from the ERG that addressing each of these would be likely to increase the ICER. Having reviewed all the evidence, the Committee concluded that there were fundamental issues with the structure of the manufacturer’s model, that the associated assumptions increased the uncertainty of the ICER, and that rectifying them would increase the ICER.

4.13 The Committee discussed the 24-week stopping rule used in the model. It noted from the results of the COMFORT trials that
response was rapid (see section 3.7). The Committee heard from the clinical specialists that 24 weeks was appropriate for the stopping rule, and they would feel comfortable in stopping the treatment if no response was observed after 24 weeks, taking into account both spleen size and symptoms. The Committee concluded that the 24-week stopping rule was appropriate.

4.14 The Committee discussed the definition of response applied in the model (35% or more reduction in spleen volume). The Committee noted the clinical specialists’ opinions that it did not reflect how they assessed response in clinical practice, and that patients could benefit from symptom relief and/or spleen size reduction with ruxolitinib. The ERG explained that in the model only patients who benefited in terms of spleen size would be in the responder health state, and those who only benefited from symptom relief (without spleen response) would be in the non-responder health state. Additionally, patients who had a spleen volume reduction but did not benefit from symptom relief would be in the responder health state and gain the associated quality-of-life benefits, despite symptoms not resolving. The Committee agreed with the clinical specialists that symptoms were of concern to patients and therefore should be taken into account in defining response in the model.

4.15 The Committee considered the costs that were incorporated into the model. The Committee noted the contribution of the high costs associated with lenalidomide and its disproportionate contribution to the overall costs of best available therapy given its negligible use. The Committee heard from the clinical specialists that lenalidomide was not often used in UK clinical practice but some patients would be treated with it. The Committee noted that the inclusion of lenalidomide in the best available therapy arm of the model was likely to bias the ICER in favour of ruxolitinib. The
Committee heard from the clinical specialists that they felt the best available therapy was otherwise representative of UK clinical practice. The Committee discussed the resource use costs (other than social care (see section 4.16 for discussion of social care costs)) in the model and the assumption that the responder health state incurred 30% of the resource use costs of the non-responder health state. The Committee heard from the clinical specialists that the responder health state would incur substantially lower costs and that 30% was plausible. The Committee concluded that the costs in the model were likely to be reasonable, subject to the caveat that lenalidomide should not be included. It further agreed that the scenarios (see section 3.26) presented by the manufacturer comparing ruxolitinib with hydroxycarbamide and with lenalidomide or thalidomide were not representative of UK clinical practice (see section 4.2).

4.16 The Committee discussed the incorporation of carer costs in the revised economic analyses provided by the manufacturer during consultation (see section 3.56). The Committee heard from the manufacturer that 17 clinicians had participated in the clinician survey. The Committee considered the 2 studies that supported the inclusion of carer costs and concluded that they did not provide evidence of how much or the type of formal care that would be needed for patients with myelofibrosis, nor the impact of ruxolitinib on the need for formal care. The Committee commented that it was not clear which costs would apply and the size of the population that would incur them. Additionally it considered it inappropriate to assume ‘responders’ incurred no carer costs. The Committee concluded that there was insufficient evidence on the quantity and nature of carer costs that would be incurred in relation to myelofibrosis. In addition, it was unclear which costs would need to be accounted for from an NHS and personal social services
4.17 The Committee considered the dose-intensity adjustment that was included in the manufacturer’s revised economic analyses (see section 3.52). It understood that a change in dose would not always lead to a change in cost because the same cost was associated with doses from 10 mg to 20 mg. The Committee acknowledged that a 5 mg dose would reduce cost, but that it was likely to be balanced out by 25 mg doses, which increase cost. The Committee commented that dose interruptions could be the important driver in reducing dosing costs. It noted that the manufacturer stated that both interruptions and dose reductions were used to estimate the dose-intensity adjustment (value is commercial-in-confidence). The Committee commented that it was not clear whether this had included all dose reductions observed or only those which lead to a cost saving (that is, from 10 mg to 5 mg), and whether increases in dose to 25 mg, which lead to a cost increase, were taken into account. The Committee acknowledged that because the estimation of dose intensity was not clear, the appropriateness of the proposed value could not be determined. The Committee discussed the impact of dose adjustments in clinical practice. Although it recognised that savings may be made, it was uncertain whether the level of savings proposed by the manufacturer would be realised in clinical practice. The Committee concluded that a dose-intensity adjustment may be appropriate and savings could be realised in clinical practice, but the value provided by the manufacturer was insufficiently robust.

4.18 The Committee considered the values of the other parameters in the manufacturer’s original and revised economic analyses. The Committee heard from the ERG that the most important drivers of
the model identified from the manufacturer’s original analysis, were the time horizon, utilities (see section 4.19) and survival (see section 4.20). The ERG explained that the definition of response in the model meant that only patients treated with ruxolitinib can be in the responder health state. Therefore, the longer the time horizon, the more relative utility benefit ruxolitinib can accrue, so a longer time horizon benefits ruxolitinib. The Committee considered the time horizon and agreed that the 10- and 15-year values were the most appropriate to use given the age and survival of the relevant myelofibrosis patients. It noted that whereas 35 years was in line with the NICE Guide to the methods of technology appraisal, in this instance the extended time period exaggerated benefits that had not been rectified elsewhere in the model (see section 3.60).

4.19 The Committee discussed the utility values applied in the model for the original and revised economic analyses. It noted the use of metastatic breast cancer utilities in the original analyses; despite the collection of health-related quality-of-life data in the key trials that would have allowed utilities to be generated by mapping these data onto the EQ-5D questionnaire. The Committee considered the utility values that had been mapped from EORTC QLQ-C30 data from COMFORT-II by the ERG. The Committee heard from the manufacturer that because 60% of the trial EORTC QLQ-C30 data were missing, any mapping was not valid. The Committee had concerns about the reliability of the data but noted that the same trial data were used by the manufacturer to validate the use of metastatic breast cancer utilities. The Committee agreed that they would be just as reliable for mapping. The Committee agreed that using the mapped utility values was the most appropriate approach and in line with the Guide to the methods of technology appraisal. However the Committee also discussed the content of EORTC QLQ-C30 and whether it appropriately accounted for the
symptoms of most concern to myelofibrosis patients (for example itch and fatigue), and concluded that it did not because itch was not included. The Committee also understood that as the model was structured around spleen size, and not symptom resolution, the quality-of-life changes associated with symptoms such as itch and fatigue would need to be accounted for in both the responder and non-responder health states, adding to the uncertainties involved in the model assumptions. The Committee also discussed the Australian utility values presented by the manufacturer in response to ACD consultation that were incorporated into the revised economic analyses. The Committee considered that these were no more certain than the breast cancer or mapped utilities, and that data elicited from patients would be preferred. Having considered all of the evidence presented the Committee concluded that it was problematic to use the mapped utilities, the other utilities presented in manufacturer’s submission or the Australian utilities, and this was made worse by the model’s structure. However it agreed that the most appropriate utility assumption lay in between the metastatic breast cancer (responder health state 0.823; non-responder health state 0.446) and the mapped trial data options (responder health state 0.754; non-responder health state 0.670).

4.20 The Committee discussed how the hazard ratios for survival were estimated in the original and revised economic analyses and the validity of the approach. It noted that in the original analyses the hazard ratios applied to the base-case responder health state were not taken from the COMFORT trials, or from the full NCT00509899 trial, but were estimated using only the MDACC data from the NCT00509899 trial, which provided a more favourable survival benefit than the data from the Mayo clinic. The Committee was concerned that the different centres in the NCT00509899 trial had different results, and that the hazard ratios were estimated using
historical controls rather than a control arm. The Committee considered the COMFORT-II data to be a more appropriate source for estimating survival hazard ratios, because the trial compared ruxolitinib with best available therapy. It acknowledged that this might underestimate the survival benefit with ruxolitinib because crossover had not been accounted for in the analysis, and considered that it would be valuable to understand the impact of accounting for crossover on the survival hazard ratios. The Committee acknowledged that in the manufacturer’s revised economic analyses (provided in response to ACD consultation) hazard ratios had been provided from the latest COMFORT-II data. The Committee recognised that these data represented only ruxolitinib patients whose condition had responded to treatment so there was a potential for bias in favour of ruxolitinib. The Committee commented that these were estimated using data from only 41 of 146 patients, and that had the whole population been used the results could have been quite different. The Committee concluded that the hazard ratios included in the revised economic analyses were the most appropriate of the estimates provided. The Committee recognised there could be a bias in favour of ruxolitinib (therefore underestimating the ICER), but acknowledged that the impact on the ICER was relatively small.

4.21 The Committee discussed the alternative plausible scenario presented by the ERG (see section 3.51), the manufacturer’s original base case (see section 3.24) and the manufacturer’s revised base case (see section 3.53). The Committee discussed the time horizon (see section 4.18), utility values (see section 4.19), and hazard ratios (see section 4.20). In addition, the Committee considered the appropriateness of excluding leukaemic transformation (in the original and revised economic manufacturer’s analyses), the manufacturer’s assumption of a beneficial effect for
ruxolitinib on leukaemic transformation (in the manufacturer’s original analysis, see section 3.20), and finally the appropriateness of excluding transfusion dependence (in the manufacturer’s original analysis). The Committee heard from the clinical specialists that leukaemic transformation was important in myelofibrosis, but that the impact of ruxolitinib on the rate of leukaemic transformation is currently unknown and therefore it should not be assumed that ruxolitinib reduces the rate of leukaemic transformation. The Committee heard from the clinical specialists that transfusions are used to manage haematological adverse events associated with myelofibrosis, and that ruxolitinib increases transfusions in the short term. The Committee concluded that the most appropriate approach would be to include leukaemic transformation, with equivalent rates applied for ruxolitinib and best available therapy (3.6%), and to include transfusion dependence in modelling the ICER.

4.22 The Committee discussed the exploratory analysis of the manufacturer’s original analysis, presented by the ERG that explored different discontinuation rates. The Committee agreed with the manufacturer’s original base case, and concluded that it is appropriate to use the COMFORT-II data to estimate initial discontinuation rates and the NCT00509899 data to estimate long-term discontinuation rates, rather than extrapolating long-term rates from the COMFORT-II data.

4.23 The Committee considered the manufacturer’s base case ICER (£74,000 per QALY gained), the ERG’s alternative scenario ICER (£149,000 per QALY gained) and the manufacturer’s revised ICER (£57,000 per QALY gained). The Committee agreed with the changes to the manufacturer’s base case that were presented in the ERG’s alternative scenario (see section 3.55) with the
exceptions of the full effect of the mapped utilities, and the full effect of using the ERG’s COMFORT-II survival estimates. The Committee considered that in the ERGs alternative scenario the utility value for the non-responder health state was likely to be too high because it did not account for symptoms such as itch, and crossover was not accounted for in estimating survival hazard ratios. The Committee acknowledged that addressing these was likely to reduce the ERG’s alternative scenario ICER. However, the Committee also recognised that addressing the structural limitations of the model (which relates to all 3 analyses) to enable disease progression, enable changes in response rates over time, enable maintenance of response to change over time, enable patients in the responder health state to have complications, and for best available therapy to change over time, would be likely to increase the ICER. The Committee noted that to estimate the most plausible ICER the uncertainties in the model structure would need to be addressed. The Committee considered the manufacturer’s revised ICER, and agreed with including the COMFORT-II hazard ratios estimated from patients who had taken ruxolitinib and whose spleen had responded. The Committee did not agree with the manufacturers approach to estimating carer costs, the dose-intensity adjustment estimate, excluding leukaemic transformation or the use of the Australian utility values. The Committee considered the ICER could be approaching £149,000 per QALY gained as presented by the ERG’s alternative scenario, but acknowledged that this may have overestimated the ICER because of the uncertainty in the utility and survival estimates. It considered the base-case ICERs presented by the manufacturer (£74,000 and £57,000 per QALY gained) were likely to have underestimated the ICER because of the structural limitations of the model. Therefore the Committee concluded that ruxolitinib was clinically effective, but
could not be considered a cost-effective use of NHS resources for treating disease-related splenomegaly or symptoms in adults with myelofibrosis.

4.24 The Committee recognised that in the ACD it stated that a subgroup of patients with myelofibrosis classified by IPSS as high-risk may meet the end-of-life criteria. The Committee discussed the high-risk analyses provided by the manufacturer as part of the revised economic analyses in response to ACD consultation (see section 3.55). The Committee recognised that it was not clear what had been included in this analysis, other than the additional carer costs. The Committee considered whether high-risk patients could be considered to meet the end-of-life criteria. The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust. The
Committee acknowledged that there was uncertainty in the prognosis of high-risk patients, because survival estimates ranged from a median of 1.3 to 2.3 years depending on the scoring system used. The Committee noted that the manufacturer had not demonstrated survival benefit in terms of additional months gained. The Committee acknowledged that although the size of the high-risk population had not been presented specifically, it was likely to be small. The Committee concluded that it had not been provided with evidence that high-risk patients met the end-of-life criteria.

4.25 The Committee considered whether ruxolitinib is an innovative treatment. The Committee agreed that ruxolitinib provided a step change in treating splenomegaly and symptoms in patients with myelofibrosis. The Committee acknowledged that ruxolitinib is a targeted treatment and manages symptoms for which there is currently no available treatment. Therefore the Committee agreed it could consider ruxolitinib to be innovative and would consider an ICER within the top end of the normal cost-effectiveness range.

4.26 The Committee discussed whether NICE’s duties under the equalities legislation required it to alter or add to its recommendations in any way. No equality issues within the scope of this appraisal were raised during the appraisal process or at the Committee meetings, and therefore the Committee concluded that no alterations or additions to its recommendations were needed.
### Summary of Appraisal Committee’s key conclusions

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td></td>
<td>4.4, 4.5, 4.7, 4.9</td>
</tr>
<tr>
<td></td>
<td>The Committee concluded that symptoms (especially itch and fatigue) and spleen size were both important outcomes. The Committee concluded that ruxolitinib was effective in reducing spleen size, and symptoms such as itch and fatigue.</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>The Committee concluded that ruxolitinib did have a negative impact on haematological outcomes in the short term, but agreed that these were manageable.</td>
<td>4.10</td>
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<td></td>
<td>The Committee noted that an overall survival benefit was observed in COMFORT-I (compared with placebo) and at 1 of the 2 centres of the NCT00509899 trial, the MDACC, but was not observed in COMFORT-II (compared with best available therapy) or at the Mayo clinic centre in the NCT00509899 trial. The Committee acknowledged that the impact of ruxolitinib on myelofibrosis progression remained unknown. The Committee concluded that it was plausible that ruxolitinib could offer a survival benefit. However, the reason for this benefit remained unclear.</td>
<td>4.23</td>
</tr>
<tr>
<td></td>
<td>The Committee considered the ICER could be approaching £149,000 per QALY gained as presented by the ERG’s alternative scenario, but acknowledged that this may have overestimated the ICER because of the uncertainty in the utility and survival estimates. It considered the base-case ICERs presented by the manufacturer (£74,000 and £57,000 per QALY gained) were likely to have underestimated the ICER because of the structural limitations of the model. Therefore the Committee concluded that ruxolitinib was clinically effective, but could not be considered a cost-effective use of NHS resources for treating disease-related splenomegaly or symptoms in adults with myelofibrosis.</td>
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</table>

### Current practice

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The treatments currently available do not specifically target myelofibrosis or splenomegaly, but are used to manage specific symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extreme itch and fatigue are important symptoms, and improving these would be beneficial to the wellbeing of patients with myelofibrosis. These should be considered as equally relevant as spleen volume.</td>
</tr>
</tbody>
</table>

### The technology

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National Institute for Health and Care Excellence

Final appraisal determination – Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis

Issue date: April 2013
<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>The Committee considered ruxolitinib to be an innovative treatment for patients with splenomegaly and myelofibrosis. The technology is a targeted treatment and offers a step change in treating splenomegaly because it manages symptoms for which there is currently no available treatment.</th>
<th>4.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
<td>There are currently no targeted treatments available to manage splenomegaly and symptoms in patients with myelofibrosis and therefore ruxolitinib would be considered a first-line treatment.</td>
<td>4.2</td>
</tr>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>The Committee recognised that ruxolitinib has an initial negative impact on haematological outcomes (anaemia, thrombocytopenia), but that this stabilises over time.</td>
<td>4.8</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>The Committee acknowledged that the 3 clinical trials presented (2 randomised controlled trials, and 1 non-randomised controlled trial) were appropriate for the decision problem. The Committee recognised that there were some differences between the populations in the clinical trials and the population that would be covered by the marketing authorisation in the UK. The Committee noted that data were missing from the COMFORT trials and it therefore had concerns about the reliability of the data.</td>
<td>4.5</td>
</tr>
<tr>
<td>Evidence for clinical effectiveness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relevance to general clinical practice in the NHS

The Committee considered the generalisability of the clinical trials for ruxolitinib to the UK population covered by the marketing authorisation. It noted that the COMFORT trials included only patients who had intermediate-2 risk or high-risk myelofibrosis, but that the marketing authorisation was not defined by risk categories; and that the proportion of patients with primary or secondary myelofibrosis in the trial was not representative of the UK population. The Committee heard from clinical specialists that ruxolitinib would mostly be used in higher-risk patients and that there was no difference in the management or outcome between primary and secondary myelofibrosis in clinical practice. The Committee concluded that the trial populations were generalisable to the patients who would be treated with ruxolitinib in UK clinical practice; that is those with intermediate-2 or high-risk myelofibrosis.

Uncertainties generated by the evidence

The Committee noted uncertainties in the survival benefit of ruxolitinib presented by the manufacturer because the survival hazard ratios were estimated using only the MDACC data from the NCT00509899 trial, which provided a more favourable survival benefit than the data from the Mayo clinic. The Committee was also concerned that the different centres of the NCT00509899 trial had different results, and that the hazard ratios were estimated using historical controls rather than a control arm, as observed within COMFORT-II.

The Committee noted some uncertainty in the relationship between spleen size and symptoms, but acknowledged that there was a trend between improvements in symptoms, and a reduction in spleen volume.

The Committee discussed the uncertainty around the most relevant measure of response. The Committee considered the appropriateness of the IWG-MRT criteria, spleen volume reduction (measured by MRI), and symptom improvements in defining response. The Committee considered that symptoms and spleen size were both important outcomes and just as relevant as meeting the IWG-MRT criteria.
### Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

There are no clinically relevant subgroups for which there is evidence of differential effectiveness.

### Estimate of the size of the clinical effectiveness including strength of supporting evidence

COMFORT-I results presented by the manufacturer showed a statistically significant increase in the proportion of patients who had a greater than 35% decrease in spleen volume with ruxolitinib compared with placebo (42% compared with 1%, p<0.001) after 24 weeks. Similar results were presented by the manufacturer for COMFORT-II. A statistically significantly larger proportion of patients had a reduction in spleen volume of 35% or more with ruxolitinib than with best available therapy (28% compared with 0%, p<0.001) after the primary end point of 48 weeks.

The manufacturer presented symptom scores from COMFORT-I. Total symptom score was measured using the modified myelofibrosis symptom assessment form, and a reduction of 50% or more was used as a measure of response. Statistically significantly more patients had a 50% or more reduction in total symptom score with ruxolitinib (45.9%) than with placebo (5.3%) at week 24 (p<0.001).

The Committee concluded that ruxolitinib was effective in reducing spleen size, and that ruxolitinib reduced symptoms such as itch and fatigue, which are associated with myelofibrosis and splenomegaly.

### Evidence for cost effectiveness

**Availability and nature of evidence**

The Committee noted the ERG’s concerns around the model structure and related assumptions including the maintenance of response and survival and discontinuation rates over time, no disease progression, no complications for patients in the responder health state, and continuation of best available therapy throughout the time horizon. The Committee concluded that there were fundamental issues with the structure of the manufacturer’s model, that the associated assumptions increased the uncertainty of the ICER, and that rectifying them would increase the ICER.
Uncertainties around and plausibility of assumptions and inputs in the economic model

The Committee recognised some uncertainty in the definition of response in the manufacturer’s model. The Committee discussed the definition applied in the model (35% or more reduction in spleen volume). The Committee noted the clinical specialists’ opinions that it did not reflect how they assessed response in clinical practice, and that patients could benefit from symptom relief and/or spleen size reduction with ruxolitinib. The Committee agreed with the clinical specialists that symptoms were of concern to patients and therefore should be taken into account in defining response in the model.

The Committee concluded that the costs in the model were likely to be reasonable, subject to the caveat that lenalidomide should not be included.

The Committee discussed the incorporation of carer costs in the revised economic analyses provided by the manufacturer during consultation. The Committee concluded that there was insufficient evidence on the quantity and nature of carer costs that would be incurred in relation to myelofibrosis, and it was unclear which costs would need to be accounted for from an NHS and personal social services perspective (NICE reference case), and therefore it could not consider these costs further.

The Committee considered the dose-intensity adjustment that was included in the manufacturer’s revised economic analyses. It understood that a change in dose would not always lead to a change in cost because the same cost was associated with doses from 10 mg to 20 mg. The Committee acknowledged that because the estimation of dose intensity was not clear, the appropriateness of the proposed value could not be determined. The Committee concluded that a dose-intensity adjustment may be appropriate and savings could be realised in clinical practice, but the value provided by the manufacturer was insufficiently robust.

The Committee discussed the utility values applied in the model. It noted the use of metastatic breast cancer utilities, despite the collection of health-related quality-of-life data in the key trials that would have allowed utilities to be generated by mapping these data onto the EQ-5D questionnaire. The Committee also discussed the
Australian utility values presented by the manufacturer in response to ACD consultation that were incorporated into the revised economic analyses. The Committee considered that these were no more certain than the breast cancer or mapped utilities, and that data elicited from patients would be preferred. The Committee concluded that using the mapped utility values was the most appropriate approach and in line with the Guide to the methods of technology appraisal.

The Committee discussed how the hazard ratios for survival were estimated in the model and the validity of the approach. It noted that the hazard ratios applied to the base-case responder health state were not taken from the COMFORT trials, or from the full NCT00509899 trial, but were estimated using only the MDACC data from the NCT00509899 trial, which provided a more favourable survival benefit than the data from the Mayo clinic. The Committee was concerned that the different centres in the NCT00509899 trial had different results, and that the hazard ratios were estimated using historical controls rather than a control arm. The Committee acknowledged that in the manufacturer’s revised economic analyses (provided in response to ACD consultation) hazard ratios had been provided from the latest COMFORT-II data. The Committee recognised that these data represented only ruxolitinib patients whose condition had responded to treatment so there was a potential for bias in favour of ruxolitinib. The Committee concluded that the hazard ratios included in the revised economic analyses were the most appropriate of the estimates provided. The Committee recognised there could be a bias in favour of ruxolitinib (therefore underestimating the ICER), but acknowledged that the impact on the ICER was relatively small.
The Committee considered the appropriateness of excluding leukaemic transformation in the manufacturer's base case, the manufacturer's assumption of a beneficial effect for ruxolitinib on leukaemic transformation in sensitivity analysis, and finally the appropriateness of excluding transfusion dependence from the manufacturer's base case. The Committee concluded that the most appropriate approach would be to include leukaemic transformation, with equivalent rates applied for ruxolitinib and best available therapy (3.6%), and to include transfusion dependence in modelling the ICER.

Incorporation of health-related quality-of-life benefits and utility values

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

The ERG explained that in the model only patients who benefited in terms of spleen size would be in the responder health state, and those who only benefited from symptom relief (without spleen response) would be in the non-responder health state. Additionally, patients who had a spleen volume reduction but did not benefit from symptom relief would be in the responder health state and gain the associated quality-of-life benefits, despite symptoms not resolving. The Committee agreed with the clinical specialists that symptoms were of concern to patients and therefore should be taken into account in defining response in the model.

The Committee acknowledged that using the EORTC QLQ-C30 data as a source for estimating mapped utilities would not take into account fatigue and itch, 2 important symptoms to myelofibrosis patients. It concluded that the most appropriate utility assumption lay in between the metastatic breast cancer and the mapped trial data options.

Are there specific groups of people for whom the technology is particularly cost effective?

Not applicable.

What are the key drivers of cost effectiveness?

The Committee heard from the ERG that the most important drivers in the model were the time horizon, utilities and survival. In the revised economic analyses, the key driver of the difference in ICER compared with the original analyses was the dose intensity adjustment.
Most likely cost-effectiveness estimate (given as an ICER)  The Committee considered the ICER could be approaching £149,000 per QALY gained as presented by the ERG’s alternative scenario, but acknowledged that this may have overestimated the ICER because of the uncertainty in the utility and survival estimates. It considered the base-case ICERs presented by the manufacturer (£74,000 and £57,000 per QALY gained) were likely to have underestimated the ICER because of the structural limitations of the model. Therefore the Committee concluded that ruxolitinib was clinically effective, but could not be considered a cost-effective use of NHS resources for treating disease-related splenomegaly or symptoms in adults with myelofibrosis.  4.24

### Additional factors taken into account

| Patient access schemes (PPRS) | Not applicable | - |
| End-of-life considerations | The Committee considered whether high-risk patients could be considered to meet end-of-life criteria. The Committee acknowledged that there was uncertainty in the prognosis of high-risk patients, because survival estimates ranged from a median of 1.3 to 2.3 years depending on the scoring system used. The Committee noted that the manufacturer had not demonstrated survival benefit in terms of additional months gained. The Committee concluded that it had not been provided with evidence that high-risk patients met the end-of-life criteria. | 4.24 |
| Equalities considerations and social value judgements | The Committee discussed whether NICE’s duties under the equalities legislation required it to alter or add to its recommendations in any way. No equality issues within the scope of this appraisal were raised during the appraisal process or at the Committee meetings, and therefore the Committee concluded that no alterations or additions to its recommendations were needed. | 4.26 |

## Implementation

### 5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Act

National Institute for Health and Care Excellence

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Issue date: April 2013
Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication] Slides highlighting key messages for local discussion.

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

There is no related guidance for this technology.

7 Review of guidance

7.1 The guidance on this technology will be considered for review in June 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.
Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Gary McVeigh
Vice Chair Appraisal Committee C, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Professor Kathryn Abel
Director of Centre for Women’s Mental Health, University of Manchester

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust
CONFIDENTIAL

Professor of Haematology, Newcastle University

**Dr Anna O'Neill**
Deputy Head of Nursing & Healthcare School/Senior Clinical University Teacher, University of Glasgow

**Dr Martin Price**
Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

**Alan Rigby**
Senior Lecturer and Chartered Statistician, University of Hull

**Dr Peter Selby**
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Dr John Stevens**
Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

**Prof Matt Stevenson**
Technical Director, School of Health and Related Research, University of Sheffield

**Dr Judith Wardle**
Lay Member

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**B  NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Melinda Goodall**
Technical Lead

**Kay Nolan**
Technical Adviser

**Lori Farrar**
Project Manager
Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) Technology Assessment Group:


B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Novartis Pharmaceuticals

II Professional/specialist and patient/carers groups:

- British Committee for Standards in Haematology
- British Society for Haematology
- Cancer Research UK
- Leukaemia CARE
- MPD Voice
- Rarer Cancers Foundation
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
III Other consultees:

- Department of Health
- Greater Manchester PCT cluster
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- MRC Clinical Trials Unit
- NHS Centre for Reviews & Dissemination and Centre for Health Economics - York
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Brian Huntley, Honorary Consultant Haematologist, nominated by Royal College of Pathologists – clinical specialist
- Dr Mallika Sekhar, Consultant Haematologist, nominated by Royal College of Physicians – clinical specialist
- Max Smith, nominated by Leukaemia Care – patient expert
- Dr Colin Clayton, nominated by MPD Voice – patient expert
D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals