Cost-effectiveness of ruxolitinib (Jakavi®) for the treatment of splenomegaly or disease-related symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.
1. Ruxolitinib (Jakavi®) is an oral therapy indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. It is an inhibitor of JAK1 and JAK2. It was granted a European licence in August 2012 and is designated an orphan drug. A final dossier was submitted by the company to the NCPE on 23rd April 2013. The company are seeking reimbursement under the high technology drugs scheme (HTDS).

2. The economic evaluation presented compared ruxolitinib with best available therapy (BAT) for the treatment of splenomegaly or disease related symptoms in adult patients with primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocytopenia myelofibrosis.

3. Two primary trials are presented as evidence of efficacy and safety; COMFORT I and COMFORT II. Both pivotal trials were randomised controlled trials in patients with an International Prognostic Scoring System (IPSS) score of 2 (intermediate-2 (2 risk factors)) or 3 (high risk (3 risk factors)). The primary endpoint in both trials was a surrogate marker for benefit; the proportion of patients with a reduction in spleen volume of 35% or more at 24 weeks (COMFORT I) and at 48 weeks (COMFORT II). Outcomes for COMFORT II were used for the economic model.

4. In COMFORT II the primary endpoint was met by 28% of patients in the ruxolitinib group versus 0% in the BAT group (P<0.001). In COMFORT I the primary endpoint was met by 41.9% of the ruxolitinib group compared to 0.7% of the placebo group (Odds ratio (OR) 134.4, 95% confidence interval (CI) 18, 1004.9, P<0.001). Neither trial was adequately powered for detecting a difference in survival. In COMFORT I the hazard ratio for survival for ruxolitinib vs. placebo at 51 weeks was 0.50 (95% CI 0.25, 0.98; P=0.04). In COMFORT II, although the median survival time had not been reached the HR was 1.01 (95% CI 0.32, 3.24) for ruxolitinib versus BAT at 61.1 weeks indicating that there was no survival advantage at this point for ruxolitinib over BAT. Three year data for COMFORT II was published in abstract form in June 2013. The HR given for this data was 0.48 (95% CI, 0.28-0.85; p=0.009).
An additional HR for responder versus non-responder was calculated for the economic model. The review group had concerns that the number of patients used to calculate this figure was small. Cervantes et al. 2009. published overall survival for patients who were not on JAK inhibitor therapy. This data was used as a surrogate for survival for non-responders. The median survival for high and intermediate risk 2 was 27 months (95% CI 23, 31) and 48 months (95% CI 43, 59) respectively.

5. The most commonly reported adverse events in both trials was thrombocytopenia and anaemia. Other adverse effects of note were an increase in infections (in the ruxolitinib groups there were 3 cases of tuberculosis overall) and three cases of fatal bleeding. Hypercholesteremia, weight gain and raised liver enzymes were also observed more often in the ruxolitinib group.

6. The model presented takes into account only those patients with IPSS classification of high risk or intermediate-2 risk (approximately 50% of myelofibrosis patients) however the drug is licensed for all classifications. A state transition Markov model was submitted which comprised of four mutually exclusive health states; responder, non-responder, discontinuation and death. The cycle lengths was 12 weeks and the time horizon was 35 years. Patients enter the model following diagnosis of myelofibrosis and receive either ruxolitinib or BAT and transition into one of the four health states. Transition probabilities were calculated based on the following clinical parameters; response rates (surrogate marker of spleen size reduction), overall survival, discontinuations, transfusion dependence, adverse events, complications of MF and leukaemic transformation.

7. The review group have concerns that responders remaining in the model for this length of time (35 years) accrue a large benefit (from both survival and HRQOL utility) and such an assumption is based on a relatively short term period and relatively few patients. Further the time horizon over which responders accrue this benefit may favour ruxolitinib as there are no responders in the BAT arm.
8. Health related quality of life was measured in the trial via the EORTC QLQ-C30 and the FACT-Lym subscales, but these were not used in the model. A valuation study was carried out in Australia which was used to calculate the utilities for the basecase. The review group noted that these utilities were not derived from an Irish population and therefore the data may not be generalisable to the Irish population. An alternative estimate from mapped utilities using the transformation published by Roskell et al. was used in a sensitivity analysis.

9. The company dossier estimated the basecase ICER of ruxolitinib versus BAT to be €70,252/QALY (incremental costs €84,292 and incremental QALY 1.20) and €71,401/LYG. Both one way sensitivity analysis and probabilistic analysis was performed. The time horizon had most impact on the ICER followed by discounting to costs and outcomes. The maximum ICER was €1,009,695/QALY at a time horizon of 24 weeks. When the dosing intensity is returned to 100% intensity rather than 81% the ICER increases to €87,558.68/QALY. There was 0% probability of cost effectiveness at a willingness to pay threshold of €45,000/QALY.

10. The annual per patient treatment cost of ruxolitinib assuming 100% compliance and is €52,405.32 per year. The company estimate that the gross budget impact (BI) will range from €190,090 (based on 3months supply) to €1,935,000 by year 5. The review group highlighted that these figures are based on treating 50% (high risk and intermediate-2) of patients. By assuming that 79% of patients are to be treated (includes intermediate-1 also), the gross BI increases to €300,343 in 2013 (24 patients) and €2,613,227 in 2017 (11 patients). The net BI (less budget impact for BAT), using eligibility of 79% of myelofibrosis population, ranges from €230,371 in 2013 to €2,308,822 in 2017. At a threshold of €45,000/QALY the 10 year Population economic risk associated with ruxolitinib, is estimated to be €21.10 million.

11. The NCPE do not consider ruxolitinib to be a cost effective treatment of splenomegaly or disease-related symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.