Cost-effectiveness of ruxolitinib (Jakavi®) for polycythaemia vera

The NCPE has issued a recommendation regarding the cost-effectiveness of ruxolitinib (Jakavi®) Following NCPE assessment of the applicant's submission, ruxolitinib (Jakavi®) is not considered cost-effective for the treatment of polycythaemia vera and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Novartis) economic dossier on the cost effectiveness of ruxolitinib (Jakavi®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **August 2016**

Summary

In April 2016, Novartis submitted a dossier examining the cost effectiveness of ruxolitinib for the treatment of patients with polycythaemia vera (PV) who are resistant or intolerant to treatment with hydroxyurea. Final data submitted by the applicant was received on 16th June 2016.

The recommended starting dose is 10mg twice daily via the oral route. Doses may be titrated upwards (to a maximum of 25mg twice daily) or downwards based on safety and efficacy.

In the submission, the comparators investigated were grouped as 'Best Available Therapy' (BAT), which included hydroxyurea, anagrelide, interferon and no treatment.

1. Comparative effectiveness of ruxolitinib

Relative efficacy outcomes for the comparison with BAT were derived from the RESPONSE study. This study was an open-label randomised controlled trial of 222 patients with PV who were resistant or intolerant to hydroxyurea and who had confirmed splenomegaly. Patients were assigned to one of two arms on a 1:1 basis, to receive either ruxolitinib 10mg twice daily or BAT, comprising of hydroxyurea, interferon, anagrelide, lenalidomide or thalidomide, or no medication. All patients received low-dose aspirin and phlebotomy as required. The primary endpoint of the trial was a composite outcome of a) the proportion of patients who achieved the absence of need for phlebotomy and b) a reduction in spleen volume. Patients randomised to the control group were eligible for crossover to the treatment group at or after week 32 – the time point for assessment of the primary end-point.

At week 32, a greater proportion of ruxolitinib-treated patients achieved haematocrit control and a ≥35% reduction in spleen volume than BAT-treated patients – 20.9% vs 0.9%; Odds Ratio (OR) 28.64 (95% CI 4.50, 1206); $p<0.0001$). A much greater proportion of patients reported an improvement in their PV symptoms of greater than 50%, in the

ruxolitinib arm compared to the BAT arm (48.6% versus 4.9%), and a greater proportion of patients achieved the composite secondary endpoint of Complete Haematological Response (CHR) in the ruxolitinib arm than the BAT arm (23.6% versus 8.9%).

2. Safety of ruxolitinib

Comparative safety versus BAT in the RESPONSE study at week 32 indicates adverse events of all types are common in both arms (95.5% in the ruxolitinib vs 93.7% in the BAT arm). However treatment-related effects were significantly higher in the ruxolitinib arm (59.1%) versus BAT (33.3%). There were a higher proportion of patients in the ruxolitinib arm who suffered serious AEs (13.6% versus 9%), and similarly, Grade 3-4 AEs occurred more frequently in the ruxolitinib arm (32.7% versus 28.8%). AEs leading to discontinuation were also higher 6.4% versus 0.9%. The important identified risks in the EMA Risk Management Plan (RMP) include myelosuppression, infections, tuberculosis and bleeding.

3. Cost effectiveness of ruxolitinib

A Markov state transition model with a 15 year time horizon, programmed in Microsoft Excel® was constructed for the cost-effectiveness analysis. The model relies on a correlation between white blood cell (WBC) control defined as WBC $\leq 10 \times 10^9$/L, a component of the CHR, and overall survival (OS) to predict the long term outcomes associated with treatment. There are three health states, 'On primary treatment', 'First subsequent treatment', and 'Death'; 'Death' is the absorbing state. The patient population under consideration are all patients with PV who are resistant to or intolerant of hydroxyurea. Patients are assumed to receive treatment in the 'On primary treatment' state and are assigned to either ruxolitinib or BAT. Within the 'On primary treatment' and the 'First subsequent treatment' states, patients can be in one of two distinct sub-states, 'White blood cell (WBC) control' or 'No WBC control', based on the CHR recorded in each treatment arm in the RESPONSE study.

Transition probabilities for death were calculated for the 'WBC control' versus 'No WBC control' group, using background survival estimates and a published HR of 4.1 from a retrospective cohort study published by Tefferi et al (2013), for the increased risk of death

for patients with 'WBC control' versus 'No WBC control'. Survival probabilities are also adjusted for the prognostic variable of hydroxyurea resistance versus intolerance, based on a published HR of 5.6 derived from a published, retrospective cohort study by Alvarez-Larran et al (2012).

Leukaemic transformations from PV occur in a proportion of patients, approximately 10-15% patients with PV according to the company submission. The risk of transformation and associated costs and changes in utility are not captured in the model. The cost of subsequent treatment for PV is included in the model. Resource use estimates are based on expert opinion. Drug acquisition costs, monitoring costs, adverse event costs, end of life costs, and costs of thrombotic events were included in the model. Patient utility was assumed to be a function of treatment status, and was calculated based on a disease specific measure (MPN-SAF) and algorithm (MF-8D).

The Review Group implemented a number of changes to the model including using different hazard ratios from the literature for adjusting for the impact of WBC control on overall survival, removing the costs and utility decrement associated with thrombotic events, implementing EQ-5D based utility values from the RESPONSE-2 trial and updating the utility value in the subsequent treatment state based on this adjustment, implementing alternative curve fits for treatment discontinuation and overall survival, and adjusting the treatment costs in the model. Implementing the preferred set of Review Group amendments in the model results in an ICER of €320,600/QALY (incremental costs €205,113, incremental QALYs 0.6398). However the RG note that there is still considerable uncertainty associated with this ICER, mainly due to the lack of clinical evidence of survival benefit. It should also be noted that the model inputs only represent a sub-population of the licensed group most likely to show greatest benefit with ruxolitinib (those with splenomegaly), and so the ICER in the licensed population would be significantly higher again.

Both deterministic and probabilistic sensitivity analyses were presented, and a number of scenario analyses were explored by the Review Group.

4. Budget impact of ruxolitinib

The cost of a 28-day supply of ruxolitinib to the HSE is €3,960.32 (excluding the Hi-tech care fee). The annual cost is estimated at €52,405.32

Based on a conservative estimate that 15.5% of the PV population would be eligible for treatment with ruxolitinib, and a market share of 60-80% for ruxolitinib, the RG estimated the 5 year gross BI for ruxolitinib of €11.69 million. The manufacturer estimates were approximately €10.7 million. Using the Review Group estimates, the cumulative net budget impact over the 5 years was €10.5million.

5. Conclusion

Following NCPE assessment of the applicant's submission, the cost effectiveness of ruxolitinib (Jakavi®) for the treatment of polycythaemia vera has not been demonstrated, and therefore is not recommended for reimbursement.