Cost-effectiveness of ruxolitinib (Jakavi®) for the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ruxolitinib (Jakavi®). Following assessment of the Applicant's submission, the NCPE recommends that ruxolitinib (Jakavi®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Novartis Pharmaceuticals) Health Technology Assessment dossier on 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 **July 2021**

Summary

In September 2020, Novartis Pharmaceuticals submitted a dossier investigating the clinical effectiveness, cost effectiveness and potential budget impact of ruxolitinib (Jakavi®) for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea (HU). Reimbursement is sought under the High Tech Drug Arrangement.

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs), JAK1 and JAK2. PV is a myeloproliferative neoplasm known to be associated with dysregulated JAK1 and JAK2 signalling. Ruxolitinib is given orally. The recommended starting dose in PV is 10 mg twice daily, and may be titrated up to a maximum dose of 25 mg twice daily. Ruxolitinib is available in tablet form in four strengths: 5 mg, 10 mg, 15 mg and 20 mg (for all, pack size 56 tablets). Treatment may be continued as long as the benefit-risk remains positive. However, treatment should be discontinued after six months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy. Discontinuation is also recommended for patients who have demonstrated some degree of clinical improvement but sustain an increase in spleen size and no longer have tangible improvement in disease-related symptoms.

In Ireland, current treatments for patients with PV who are resistant to or intolerant of HU include interferon, pegylated-interferon, anagrelide, continuation of HU, or no treatment. For the purpose of this submission, these treatments are collectively referred to as 'best available therapy' (BAT).

1. Comparative effectiveness of ruxolitinib

Direct clinical evidence

The clinical efficacy and safety of ruxolitinib was examined in the RESPONSE and RESPONSE-2 trials. Both are phase III, open-label trials which randomised adult patients with PV who were resistant to or intolerant of HU, to receive either ruxolitinib or BAT. The main difference between trials related to study populations: RESPONSE recruited patients with PV with splenomegaly, whereas RESPONSE-2 recruited those without splenomegaly. Results of final five-year analyses for both trials were available. A key methodological concern in both trials was the lack of long-term comparative efficacy data due to crossover, with patients in

the BAT arms in RESPONSE and RESPONSE-2 potentially becoming eligible to switch to treatment with ruxolitinib after 32 and 28 weeks, respectively. In RESPONSE, 98/112 (87.5%) patients randomised to BAT subsequently switched to ruxolitinib. In RESPONSE-2, 58/75 (77.3%) patients randomised to BAT switched.

For RESPONSE, the primary endpoint was the proportion of patients achieving a 'primary response' (defined as ineligibility for phlebotomy and reduction in spleen volume) at week 32. Of the patients randomised to ruxolitinib, 25/110 (22.7%) achieved primary response at week 32 versus 1/112 (0.9%) patients randomised to BAT (difference 21.8% [95% CI: not reported; p-value<0.0001]). The Kaplan Meier (KM) estimated probability of maintaining a primary response from week 32 until week 256 was 0.74 (95% CI: 0.51, 0.88). At the final analysis (256 weeks), 10/110 (9.1%) patients in the ruxolitinib group had died, versus 9/112 (8.0%) patients in the BAT group. For RESPONSE-2, the primary endpoint was the proportion of patients achieving haematocrit (Hct) control (defined as ineligibility for phlebotomy) at week 28. A greater proportion of patients randomised to ruxolitinib achieved Hct control at week 28 than those randomised to BAT (ruxolitinib: 46/74 [62.2%] vs. BAT: 14/75 [18.7%]; difference 43.5% [95% CI: 29.4, 57.6]). In terms of overall survival (OS), the KM-estimated five-year OS in the ruxolitinib arm was 95.8% (95% CI: 87.4, 98.6), and in the BAT arm was 90.7% (95% CI: 80.3, 95.7). Comparisons of efficacy from both trials are limited by crossover. There is also uncertainty as to how the surrogate primary endpoints relate to clinically meaningful long-term clinical outcomes.

Indirect clinical evidence

In the absence of direct comparative evidence for the efficacy of ruxolitinib versus BAT beyond 28/32 weeks, the Applicant included details of an indirect treatment comparison (ITC) of OS for ruxolitinib versus BAT, which was used to estimate long-term comparative efficacy and populate the cost-effectiveness model. Data from the RESPONSE trial (ruxolitinib) and the Spanish GEMFIN registry (BAT) were used to inform the analysis. Eligible patients from both the RESPONSE trial and the GEMFIN registry were matched using propensity score matching. Propensity scores were calculated using four covariates which were selected based on input from clinicians and data considerations: age, sex, history of thrombosis, and cytopaenia at lowest HU dose. The Review Group was concerned that other

prognostic and/or effect-modifying patient characteristics not included in the propensity score (for example the presence of splenomegaly at baseline, and HU resistance versus intolerance) could remain imbalanced between treatment groups after matching, and potentially bias the results of the comparison. The primary analysis demonstrated a statistically significant improvement in OS for patients treated with ruxolitinib compared to BAT, with an estimated HR of 0.33 (95% CI: 0.14 to 0.81). The Applicant indicated that it was not possible to include data from RESPONSE-2 in this analysis due to the immaturity of the data at the time of analysis. The Review Group note that it is uncertain if the estimated treatment effect of ruxolitinib would be generalizable to the broader population of patients with PV. The median follow-up for both the GEMFIN and RESPONSE populations does not exceed five years; it is unknown if the estimated treatment effect of ruxolitinib will be maintained beyond this time.

2. Safety of ruxolitinib

Safety data for ruxolitinib in adult patients with PV is sourced from the RESPONSE and RESPONSE-2 trials. The safety profile of ruxolitinib has also previously been evaluated in patients with myelofibrosis. The known adverse event profile of ruxolitinib includes haematologic adverse events (myelosuppression, including anaemia, thrombocytopenia and neutropenia, and haemorrhage) and non-haematologic adverse events (including infections [herpes zoster, urinary tract infections and tuberculosis], non-melanomatous skin cancer, and progressive multifocal leukoencephalopathy).

3. Cost effectiveness of ruxolitinib

A partitioned survival model was submitted by the Applicant, which specified three health states for patients receiving ruxolitinib ('On-treatment with ruxolitinib', 'Off-treatment with ruxolitinib' and 'Death') and two states for patients receiving BAT ('On-treatment with BAT' and 'Death'). Costs and outcomes were modelled separately for the 'PV with-splenomegaly' and 'PV without splenomegaly' populations, using data from RESPONSE and RESPONSE-2, respectively. Costs and utility decrements associated with thromboembolic events were also included in the model. Patients who discontinue ruxolitinib treatment were subject to the same costs, utilities and rates of thromboembolic events as those treated with BAT. The Review Group noted that transformation to myelofibrosis (MF) and/or acute myeloid

leukemia (AML) were not included in the model. The Applicant cited lack of appropriate data as the reason for this. These conditions affect a considerable number of patients with PV and are associated with substantial costs and reduced quality of life.

Parametric extrapolations of 'time-on-treatment' curves (for ruxolitinib only) and OS curves were used to estimate health state occupancy in each cycle. For BAT, patients were assumed to remain on treatment for life, with patients who discontinue one component treatment assumed to switch to another, so 'time on treatment' was not modelled. Data from patients in the GEMFIN registry, matched to RESPONSE ('PV with-splenomegaly') and RESPONSE-2 ('PV without splenomegaly'), was used to model OS in the BAT arm. The relative treatment effect of ruxolitinib versus BAT from the ITC was applied to the BAT OS model in order to estimate OS for ruxolitinib, with the assumption that the treatment effect would be maintained over a lifetime horizon. There is considerable uncertainty associated with this assumption; the NCPE-adjusted base case implements a treatment-waning effect to reflect this uncertainty. Discontinuation rates were higher in RESPONSE compared with RESPONSE-2, and patients in the 'PV with splenomegaly' population therefore spend less time in the 'On treatment with ruxolitinib' state over the model time horizon. It is unclear whether or not this difference will be reflected in clinical practice.

The utility values used in the Applicant's base case were derived from data collected during the RESPONSE study using the MF-8D algorithm, which uses components of the generic EORTC QLQ-C30 and disease-specific MPN-SAF instruments to generate a utility value. Utility values derived using the EQ-5D instrument were available from the RESPONSE-2 study. The MF-8D algorithm is subject to a number of limitations, and in line with national guidelines, the use of a generic, preference-based measure of utility values is preferred. The NCPE-adjusted base case therefore uses utility values derived using EQ-5D data from RESPONSE-2.

The results of the NCPE-adjusted base case and Applicant's base case cost-effectiveness models are presented in Table 1 and Table 2, respectively.

Table 1 NCPE-adjusted base case cost-effectiveness analysis

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Ruxolitinib	520,334	10.43			
BAT	52,889	8.64	467,445	1.79	261,862

BAT: Best available therapy; ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2 Applicant's base case cost-effectiveness analysis*

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Ruxolitinib	526,314	11.50			
BAT	62,951	8.66	463,363	2.84	163,148

*Applicant's corrected base case following preliminary review.
BAT: Best available therapy; ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
Figures in the table are rounded, and so calculations will not be directly replicable.

The probabilities of cost-effectiveness at the €20,000/QALY and €45,000/QALY thresholds were 0% under both the Applicant and Review Group's preferred cost-effectiveness assumptions.

There is much uncertainty surrounding the Applicant's assumption of the lifetime duration of the treatment effect of ruxolitinib in terms of OS. The median OS follow-up from each of the studies used to estimate the relative effectiveness was less than five years. Under the NCPE-adjusted base case, the treatment effect of ruxolitinib in terms of OS was assumed to wane from five years to 0% at approximately 10 years. When the treatment effect is maintained over the lifetime, the NCPE-adjusted base case results in an ICER of €209,754 per QALY. When the treatment effect is reduced to 0% at five years, the ICER increases to €322,118 per QALY. The Review Group notes that relative effectiveness was estimated using data from the RESPONSE trial, which recruited patients with splenomegaly only. It is unknown whether or not the treatment effect is generalizable to patients without splenomegaly, who make up the majority of the target population. It is not possible to quantify the impact of this uncertainty on the cost-effectiveness results. The model does not account for transformation to MF and/or AML, which is also source of considerable structural uncertainty.

4. Budget impact of ruxolitinib

Based on dosing data from the RESPONSE trial, the expected annual cost to the HSE per patient for ruxolitinib is €45,829.02 (VAT not applicable). In the Applicant's base case budget impact analysis, the eligible population was estimated based on clinical opinion obtained for

a previous submission in 2015 (annual incidence 60 patients; prevalence ranged from 475 patients in Year 1 to 496 patients in Year 5). Additional clinical opinion was sought by the Applicant in 2020 for this submission. It was noted that the population estimates obtained at this time were aligned with published international epidemiologic data (annual incidence ranged from 100 patients in Year 1 to 104 patients in Year 5; prevalence ranged from 1,247 patients in Year 1 to 1,303 patients in Year 5). The NCPE-adjusted base case is calculated using these population estimates.

The Applicant projected a five-year cumulative gross budget impact for ruxolitinib of €12.68 million, a five-year cumulative net drug budget impact of €11.97 million, and a five-year cumulative net health budget impact of €11.70 million. The net drug budget impact accounted for cost offsets due to displacement of BAT, and the net health budget impact accounted for offsets in costs relating to monitoring, concomitant interventions and the management of adverse events and thromboembolic events. The NCPE-adjusted base case projected a five-year cumulative gross budget impact for ruxolitinib of €32.02 million, a five-year cumulative net drug budget impact of €30.22 million, and a five-year cumulative net health budget impact of €29.55 million.

5. Patient organisation submission

A patient organisation submission was received from MPN Voice.

6. Conclusion

The NCPE recommends that ruxolitinib (Jakavi®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.