Cost-effectiveness of midostaurin (Rydapt®) (with daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy) followed by midostaurin monotherapy for up to 12 months, for the first-line treatment of newly diagnosed adult patients with FLT3 mutation-positive acute myeloid leukaemia.

The NCPE has issued a recommendation regarding the cost effectiveness of midostaurin (Rydapt®) (with daunorubicin & cytarabine induction and high dose cytarabine consolidation chemotherapy) followed by midostaurin monotherapy for up to 12 months for the above indication. The NCPE recommends that midostaurin (Rydapt®) 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Novartis Ireland) economic dossier. 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 drugs for cancer the NCPE recommendation is also considered by the National Cancer Control Programme 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 **December 2019**

Summary

In December 2018, Novartis Ireland made a submission on midostaurin (Rydapt®) (with daunorubicin & cytarabine induction and high dose cytarabine consolidation chemotherapy) followed by midostaurin monotherapy for up to 12 months, for the first-line treatment of newly diagnosed adult patients with FLT3 mutation-positive acute myeloid leukaemia. Final data, required by the NCPE, was received on 11 November 2019.

Midostaurin is an oral, type III, multi-target inhibitor of FLT3 and other receptor tyrosine kinases. The recommended dose is 50 mg orally twice daily on days 8 to 21 of the induction and consolidation 28-day cycles. Then, for patients in complete response, 50 mg twice daily every day as monotherapy until relapse, for up to twelve 28-day cycles. The recommended co-prescribed regimens of daunorubicin and cytarabine are not specified in the licence; however, the regimens used in the pivotal study (RATIFY) are described therein.

1. **Comparative effectiveness of midostaurin (with daunorubicin and cytarabine)**

RATIFY was a placebo-controlled, double-blind, phase III randomised controlled trial. Eligible patients (18 to 59 years) with newly diagnosed FLT3 mutation-positive AML (n=717) were randomised 1:1 to induction with daunorubicin 60 mg/m^2/day (days 1 to 3) and cytarabine 200 mg/m^2/day (days 1 to 7) ('daunorubicin & cytarabine 3 + 7') with midostaurin 50 mg twice daily days 8 to 21 (midostaurin arm) or with placebo (standard of care arm). Patients who had not achieved complete remission underwent a second induction cycle. Patients who achieved complete remission after induction received four 28-day cycles of consolidation with high-dose cytarabine (3000 mg/m^2 every 12 hours on days 1, 3, and 5) with midostaurin (midostaurin arm) or placebo (standard of care arm) on days 8 to 21. During maintenance, patients received either midostaurin or placebo for up to twelve 28-day cycles (according to randomisation). Stem-cell transplantation (SCT) was not part of the protocol and was performed at investigator discretion.

The primary end point was overall survival. At the April 2015 cut-off (median follow-up of 60.2 months), the overall survival hazard ratio (HR) = 0.77 (95% CI 0.63 to 0.95); p=0.0078. Probabilities of survival at 3 years were 54% (95% CI 0.49 to 0.59) vs. 47% (95% CI 0.41 to 0.52). At 5 years, they were 51% (95% CI 0.45 to 0.56) vs. 43% (95% CI 0.38 to 0.49). Median

event free survival was 8.2 months vs. 3.0 months, HR = 0.78 (95% CI 0.66 to 0.93); p= 0.002. Complete remission (within 60 days of treatment initiation) was achieved in 58.9% vs. 53.5%; one-sided p value = 0.073. Median disease free survival was 26.7 months vs. 15.5 months, HR = 0.71 (95% CI 0.55 to 0.92); p = 0.005. In total, 59.4% and 55.2% of patients in the respective arms underwent SCT. Results for overall survival (censored by SCT) were consistent with the results of the primary endpoint. Overall survival did not differ significantly according to treatment arm within each subgroup of FLT3 mutation (TKD, ITD high ratio and ITD low ratio). At the September 2016 cut-off, the overall survival HR = 0.787 (95% CI 0.641 to 0.966); p=0.0109.

We note that the 'daunorubicin & cytarabine 3 + 7' regimen is not fully reflective of all potential comparators. On request, the Applicant updated the cost effectiveness model to include the 'daunorubicin & cytarabine 3 + 10' induction regimen; however, this makes minimal difference to cost-effectiveness outputs.

The Applicant performed network meta-analyses to facilitate a comparison with gemtuzumab ozogamicin (with daunorubicin & cytarabine) for a scenario analysis. No significant difference in efficacy was detected with midostaurin (with daunorubicin & cytarabine induction and high dose cytarabine consolidation) followed by midostaurin monotherapy vs. gemtuzumab ozogamicin (with daunorubicin & cytarabine).

The EUnetHTA Joint Action (PTJA01; November 2017) assessment states that the effect size of midostaurin in patients over 60 years remains unknown given limited evidence from a single-arm phase II trial (AMLSG 16-10).

2. Safety of midostaurin (with daunorubicin and cytarabine)

The RATIFY safety set (n=680) comprised all patients who received at least one dose of study drug. All patients, except one in the midostaurin arm, experienced a grade 3-4 adverse event. Grade 3-4 infections occurred in 54.2% vs. 52.5% of the midostaurin and standard of care arms respectively. Grade 3-4 bleeding events occurred in 11.9% vs. 9.9%. Grade 3-4 febrile neutropenia occurred in 83% of both arms. The most frequent non-haematologic grade 3-4 adverse events in the midostaurin arm were device-related infections (16.2%),

diarrhoea (15.7%) and exfoliative dermatitis (13.6%), and in the standard of care arm were hypokalaemia (17.0%), diarrhoea (15.2%) and pneumonia (14.0%). Treatment was discontinued due to grade 3-4 adverse events in 6.1% and 4.5% of the respective arms. A serious adverse event was experienced by 47% and 48.7% of the respective arms. Incidence was generally balanced with the exception of dermatitis exfoliative (2.9% vs. 0.3%) and hypotension (2.9% vs. 0.3%). The overall frequency of QT prolongation events was 19.2% and 16.8% in the respective arms.

The EUnetHTA Joint Action (PTJA01; November 2017) assessment notes that deaths during study treatment and 30-day follow-up periods have occurred more frequently in patients over 60 years. It concludes that further research is required in the older population.

3. Cost effectiveness of midostaurin (with daunorubicin and cytarabine)

The perspective is that of the HSE. Cost effectiveness is investigated using a lifetime partitioned survival model. The model is generally aligned with RATIFY; it comprises five health states (Induction/Diagnosis, Complete Remission, SCT, Relapse and Mortality). Direct evidence (vs. daunorubicin & cytarabine induction then high dose cytarabine consolidation) was derived from RATIFY (full analysis set; n=717). The proportion of patients in each state over time was estimated from Kaplan-Meier survival functions. The time-to-complete remission curve informed transitions from this state for SCT, relapse and mortality. Following trial cut-off, the proportion of patients remaining in the complete-remission state was extrapolated based directly on overall survival extrapolation data. The same overall survival extrapolation is applied to patients who have relapsed and to patients who are in remission. This is a model limitation. In the original submission, the SCT rate was derived from the individual trial arms; the Review Group have assumed a pooled rate in our preferred base case. It was assumed that no further SCT events would occur after the trial duration. Also, it was assumed that patients who underwent SCT died at the same rate as the overall surviving population after trial cut-off. The Review Group believe that such assumptions are not fully supported by evidence within the submission. During the course of the evaluation, the Applicant updated the extrapolation of the overall survival data. A piecewise model was fitted from the last event (Sept 2016 cut-off). It is assumed that people who were alive after 10 years were cured; a 2.5 multiplier (based on a UK Leukaemia

national database) was applied to a mortality rate derived from the general population. There is uncertainty regarding the true increase in mortality.

In general, there is a high level of uncertainty associated with utility values input into the model. Sensitivity analyses do not sufficiently explore this uncertainty. During the course of the evaluation, the Applicant updated the model to include Irish cost data (drug acquisition, SCT, routine disease-related costs, FLT3 mutation testing, management of adverse events and salaries). Also, as requested, the Applicant modified assumptions pertaining to wastage, dose intensity and number of secondary therapy cycles. Further, the Applicant updated methodologies used to convert non-Irish costs and to inflate costs.

An annual discount rate of 5% is applied to costs and outcomes.

All cost-effectiveness and budget-impact outputs reported here assume the list price for midostaurin. The Applicant submission includes a proposed confidential discount. All outputs are sensitive to this discount, however, they are not reported here.

The Review Group preferred base case assumes that the SCT rate is derived from pooled RATIFY data. The ICER (vs daunorubicin & cytarabine induction then high dose cytarabine consolidation) is €114,506/QALY (incremental cost = €105,864/incremental QALY= 0.92). One-way sensitivity analyses indicate that this ICER is most sensitive to changes in the complete remission rate, the SCT rate, the hazard ratio (overall survival), the duration of maintenance therapy, the cost of long-term routine care and the utility (complete remission). Scenario analyses indicate that the ICER is most sensitive to the choice of overall survival extrapolations, the discount rate and the model time horizon. Probabilities of cost effectiveness are 9% (at €20,000/QALY) and 20% (at €45,000/QALY); the mean ICER is €102,328/QALY.

Under the Applicant's proposed base case (SCT rates derived from individual trial arms) the ICER is €72,954 /QALY (€67,955/ 0.93).

A scenario analysis, facilitated by network meta-analysis, investigates cost effectiveness vs. gemtuzumab ozogamicin (with daunorubicin & cytarabine). The ICER is €189,337/QALY (€42,429/ 0.22) under the Review Group's preferred assumption (regarding pooled SCT

rates). Under the Applicant's proposed base case (SCT rates derived from the individual trial arms) the ICER is €193,761/QALY (€43,858/0.23).

4. Budget impact of of midostaurin (with daunorubicin and cytarabine)

For this indication, midostaurin is supplied as 25 mg soft capsules, at a price to wholesaler of €6,877.10 per pack (56 capsules). With rebate, mark-up and patient care-fees, the cost to the HSE is €7,111.06 per-pack. The per-patient cost of treatment is about €200,887.

The Review Group have changed a number of the assumptions in the submitted budget-impact model regarding the eligible population and market share. Despite this, the number of patients predicted by the model (i.e. 8 in Year 1, increasing to 18 in Year 5) is likely to be low. The Applicant derives first-line treatment consumption data from the individual trial arms of RATIFY. Under these assumptions, it is estimated that the 5-year cumulative gross budget impact (for midostaurin) is €5.43 million (€0.51 million in Year 1, increasing to €1.40 million in year 5). The 5-year cumulative gross budget impact for treatment with midostaurin (with daunorubicin & cytarabine) is about €5.68 million (€0.53 million in Year 1, increasing to €1.46 million in Year 5). The 5-year cumulative net budget impact of treatment with midostaurin (with daunorubicin & cytarabine) will be about €5.45 million (€0.51 million in Year 1, increasing to €1.40 million in Year 5). There are concerns that the use of first-line treatment consumption data may result in an underestimation of budget impact. In a conservative scenario, the Review Group have assumed 100% consumption for first-line treatment costs (i.e. assuming all patients receive induction, consolidation and maintenance). It is estimated that the 5-year cumulative gross budget impact (for midostaurin) is €14.06 million (€1.68 million in Year 1, increasing to €3.54 million in Year 5). The 5-year cumulative gross budget impact for treatment with midostaurin (with daunorubicin & cytarabine) is about €14.41 million (€1.72 million in Year 1, increasing to €3.63 million in Year 5). As midostaurin is an add-on therapy, under the assumption of 100% consumption across treatment arms, the net budget impact is equivalent to the gross budget impact (for midostaurin).

5. State if any patient submissions were received, and name submitting organisations.

No patient organisation submissions were received during the course of this appraisal.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that midostaurin (Rydapt®) (with daunorubicin & cytarabine induction and high dose cytarabine consolidation) followed by midostaurin monotherapy for up to 12 months, not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. *

Of note, the EUnetHTA Joint Action (PTJA01; November 2017) assessment notes that efficacy and safety data pertaining to the use of midostaurin in patients over 60 years remains limited.

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