Cost-effectiveness of gilteritinib (Xospata®) as monotherapy for the treatment of adult patients who have relapsed or refractory (R/R) acute myeloid leukaemia (AML) with a FMS-like tyrosine kinase 3 (*FLT3*) mutation.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of gilteritinib (Xospata®).

Following assessment of the Applicant's submission, the NCPE recommends that gilteritinib (Xospata®) as monotherapy for the treatment of adult patients who have R/R AML with a FLT3 mutation not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Astellas) economic dossier on the cost effectiveness of gilteritinib (Xospata®). 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.

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

National Centre for Pharmacoeconomics **March 2021**

Summary

In June 2020, Astellas submitted a dossier examining the cost-effectiveness of gilteritinib as monotherapy for the treatment of adult patients who have relapsed or refractory (R/R) acute myeloid leukaemia (AML) with a FMS-like tyrosine kinase 3 *(FLT3)* mutation. Gilteritinib was granted marketing authorisation by the European Commission for this indication in October 2019. Gilteritinib is a protein kinase inhibitor that inhibits multiple receptor tyrosine kinases, including FLT3.

The recommended starting dose of giltertitnib is 120mg once daily orally. In the absence of a response after four weeks of treatment, the dose can be increased to 200mg once daily, if tolerated or clinically warranted. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to six months should be considered to allow time for a clinical response. Gilteritinib treatment may be re-initiated in patients following HSCT. Before taking gilteritinib, patients with R/R AML must have confirmation of a *FLT3-ITD* or *FLT3-TKD* mutation using a validated test. The Applicant is seeking reimbursement under the High Tech Drug Arrangement.

The current goals of treatment in AML are to achieve remission to make the patient eligible for a haematopoietic stem cell transplant (HSCT), as this is the main curative treatment option available. Generally, only patients who are in complete response (CR) to treatment are eligible for HSCT. Patients who do not achieve CR after induction treatment or experience disease relapse after an initial response i.e., those with R/R AML, generally receive a salvage chemotherapy regimen (fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin (FLAG-IDA) or azacitidine). Patients who respond to treatment and achieve CR may be considered eligible for HSCT at any point in the treatment pathway. Patients with R/R AML who are not receiving salvage chemotherapy will receive best supportive care (BSC).

1. Comparative effectiveness of gilteritinib (Xospata®)

Direct comparative evidence for the effectiveness of gilteritinib versus salvage chemotherapy, in patients with R/R AML, is available from the ADMIRAL open-label, phase III, randomised, controlled trial.

Patients were randomised in a 2:1 ratio to receive either gilteritinib 120mg daily or one of four salvage chemotherapies which were pre-selected by investigator's prior to randomisation. Options for salvage chemotherapy included azacitidine, FLAG-IDA, low dose cytarabine (LoDAC) or mitoxantrone in combination with etoposide and cytarabine (MEC). Patients received gilteritinib, LoDAC or azacitidine until unacceptable toxicity or disease progression. Patients receiving FLAG-IDA or MEC could receive a maximum of two treatment cycles. Patients receiving gilteritinib could undergo HSCT without leaving the study. Gilteritinib could be resumed after HSCT. In the salvage chemotherapy arm, HSCT was considered an off-study treatment. The different status of HSCT in the two study arms results in an unequal comparison between treatments which could influence the magnitude of any clinical benefit. The co-primary endpoints were CR/complete remission with partial haematological recovery (CRh) and overall survival (OS). Secondary endpoints included event free survival (EFS), CR rate and adverse events (AEs). Health-related quality of life (HRQoL) measures were also collected using the EuroQoL Group-5 Dimension (EQ-5D-5L) questionnaire. Two interim analyses and one final analysis were planned. The first interim analysis (clinical cut-off date (CCOD): 7 August 2017) evaluated the co-primary endpoint of CR/CRh rate in the gilteritinib arm only. The second interim analysis (CCOD: 16 October 2017) and final analysis (CCOD: 17 September 2018) analysed the co-primary endpoint of OS in addition to the other endpoints. The median duration of follow-up at the final analysis was 17.8 months. A further unplanned ad-hoc analysis was conducted in September 2019 (unpublished). Final efficacy analyses were performed in the intention-to-treat (ITT) population.

At the final analysis, median OS was 9.3 months (95% CI 7.7 to 10.7) in patients receiving gilteritinib and 5.6 months (95% CI 4.7 to 7.3) in patients receiving salvage chemotherapy; hazard ratio (HR) = 0.64 (95% CI 0.49 to 0.83). Median EFS was 2.8 months (95% CI 1.4 to 3.7) in patients receiving gilteritinib and 0.7 months (95% CI 0.2 to not estimable (NE)) in

patients receiving salvage chemotherapy; HR = 0.79 (95% CI 0.58 to 1.09). It should be noted that data for relapse events were not routinely collected in patients receiving high intensity salvage chemotherapy, i.e., MEC and FLAG-IDA, during follow-up with almost all patients having their data censored for EFS at one to two months post-randomisation. The EQ-5D-5L results indicate that there does not appear to be a clinically meaningful detriment or improvement in quality of life when comparing gilteritinib to salvage chemotherapy.

In the absence of direct head-to-head evidence for the comparison with BSC, a naive treatment comparison was performed, using a retrospective cohort study to inform effectiveness data for BSC. The Review Group had concerns that a naive comparison would lead to a high degree of uncertainty in the model for this comparison.

2. Safety of gilteritinib (Xospata®)

In the ADMIRAL trial, the safety population was defined as patients who received at least one dose of trial treatment. Safety data are reported for the September 2018 final analysis. The median duration of exposure to trial treatment was 126 days in patients receiving gilteritinib and 28 days in patients receiving salvage chemotherapy. Separate safety data were not available for each of the four salvage chemotherapy regimens.

AEs were more common in patients receiving gilteritinib (any 100%; grades 3+ 95.9%) compared to those receiving salvage chemotherapy (any 98.2%; grades 3+ 86.2%). The most frequently reported grade 3 or above AEs were febrile neutropenia (gilteritinib: 45.9%; salvage chemotherapy: 36.7%), anaemia (gilteritinib: 40.7%; salvage chemotherapy: 30.3%), thrombocytopenia (gilteritinib: 22.8%; salvage chemotherapy: 16.5%), platelet count decreased (gilteritinib: 22.0%; salvage chemotherapy: 24.8%) and neutrophil count decreased (gilteritinib: 17.1%; salvage chemotherapy: 11.0%).

The most frequently reported serious adverse events (SAEs) in the gilteritinib arm were febrile neutropenia (30.9%), AML (13.4%), pyrexia (13.0%) and pneumonia (10.6%). Drug related SAEs of special safety interest were experienced by 10.6% of patients receiving gilteritinib, most frequently alanine aminotransferase increased (4.5%) and aspartate aminotransferase increased (4.1%).

Drug related AEs that led to death were observed in 4.1% of patients receiving gilteritinib and 4.6% receiving salvage chemotherapy.

The safety results from the ADMIRAL trial were in line with those observed in other trials of gilteritinib.

3. Cost effectiveness of gilteritinib (Xospata®)

A cost-utility analysis was implemented using a decision-tree component to stratify patients based on their HSCT status, followed by two separate three-state partitioned survival models to predict long-term survival status of the target population conditional on their HSCT status. The model assumed a cycle length of one-month and a lifetime horizon. A half cycle correction was applied.

All patients enter the model in the 'treatment alone without HSCT' health state. A proportion of patients, corresponding to the HSCT transplant rate in ADMIRAL transition to the 'EFS with HSCT' state after the average time to HSCT observed in ADMIRAL has elapsed. Patients with and without HSCT are modelled separately from this point. Patients receiving gilteritinib or salvage chemotherapy enter the partitioned survival model in the EFS health states, where they remain until they experience an event (transition to the post-event health states) or they experience death. Patients remain in the post-event health states until death. Patients receiving BSC were assumed to have a low likelihood of achieving remission and thus a HSCT. Consequently, all patients receiving BSC were assumed to enter the model in the post-event without HSCT health state. After 25 months the model assumes that all patients who remain alive after HSCT are cured and follow a standard mortality rate (SMR) of two, i.e., double the SMR. This cure point was informed by observing the inflection point of longer-term survival trajectories reported in the literature and Irish clinical opinion sought by the Applicant. The two-year cure point is consistent with clinical opinion sought by the Review Group. In the model, cured patients incurred lower costs and higher utilities than non-cured patients.

Costs and utilities were allocated to each health state. The partitioned survival approach uses the "area under the curve" approach, where the number of patients in each health state at a given time is taken directly from survival curves fitted to clinical trial data.

Clinical data for gilteritinib and the comparison with salvage chemotherapy in the model base case were obtained from the ADMIRAL trial. As it was not possible to separate azacitidine and FLAG-IDA results in the ADMIRAL trial from those of the other salvage chemotherapy regimens, a blended/weighted comparator of salvage chemotherapy was used for the efficacy data in the model. Costs were applied to reflect the use of azacitidine and FLAG-IDA in Irish clinical practice. In the Applicant base case BSC was also included in the weighted comparator. Costs for BSC were not included in the model.

Utilities were included for each health state (with and without HSCT), and for long-term survivors' post HSCT. All health state specific utilities were derived directly using HRQoL data from the ADMIRAL trial. Utilities were assumed to be independent of treatment group. The utility associated with the long-term survivors was assumed to equal the general population and included an adjustment for age. Disutilities were included for HSCT, age and AEs and were obtained from the literature.

The Review Group considers that relevant costs were included in the model. Costs included in the model were treatment (drug acquisition and administration), AE, HSCT, medical costs for each health state, *FLT3* mutation testing, post-progression treatment, and terminal care costs. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group suggested changes to the Applicant base case based on plausible alternative assumptions. These included removing BSC from the weighted comparator and including it in a separate analysis, removing the post-HSCT benefit for gilteritinib and using the log-logistic in preference to the Gompertz to extrapolate post-HSCT OS. The NCPE adjusted ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1: NCPE adjusted base case*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Weighted comparator (FLAG-IDA & AZA)	130,078	0.848	153,350
BSC	185,852	2.148	86,531

AZA: azacitidine; **BSC:** best supportive care; **FLAG-IDA:** fludarabine, cytarabine, granulocyte colony-stimulating factor & idarubicin; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality adjusted life year.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2: Applicant base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Weighted comparator (FLAG-IDA, AZA & BSC)	151,692	1.832	82,817
Weighted comparator (FLAG-IDA & AZA)	131,561	1.246	105,575
BSC	187,463	2.573	72,856

ATEZO: atezolizumab; **CE:** carboplatin + etoposide; **CiE:** cisplatin + etoposide; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality adjusted life year.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

The Review Group acknowledged the limitations and uncertainty with post-HSCT costs and benefits in the model and for the NCPE adjusted base case have provided the most conservative estimate for decision making. Removing both post-HSCT benefit and costs from the NCPE adjusted base case results in an ICER of €111,406 per QALY compared to salvage chemotherapy and €69,966 per QALY compared to BSC.

From the probabilistic sensitivity analysis, there was zero probability of gilteritinib being cost-effective compared to a weighted comparator (FLAG-IDA and azacitidine) or BSC at thresholds of €20,000 per QALY and €45,000 per QALY, using the NCPE adjusted base case.

Many scenario analyses were presented addressing structural uncertainty and model assumptions. The NCPE-adjusted base case ICERs were most sensitive to assumptions surrounding the 'cure-point', parametric distribution for OS, the use of external data to inform post-HSCT OS and the inclusion of post-HSCT gilteritinib cost.

4. Budget impact of gilteritinib (Xospata®)

The price to wholesaler of gilteritinib is €17,300 for a pack of 84 x 40mg tablets. The average treatment cost per patient, including all relevant fees, mark-ups and rebates, is estimated as

€142,317; assuming 100% dose intensity and the mean number of treatment cycles observed in the ADMIRAL trial.

The Applicant estimated that nine patients would be treated with gilteritinib in year one, rising to 14 in year five. The projected cumulative five-year gross budget impact is €8.8 million.

The Applicant also presented a net drug budget impact assuming gilteritinib will displace azacitidine, FLAG-IDA and BSC. BSC was assigned zero costs. The projected cumulative five-year net budget impact is €8.4 million.

5. Patient submissions

No patient submissions were received in support of the application.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that gilteritinib (Xospata®) as monotherapy for the treatment of adult patients who have R/R AML with a FLT3 mutation 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.