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CADTH DRUG REIMBURSMENT REVIEW

# Pharmacoeconomic Report

## GILTERITINIB (XOSPATA)

(Astellas Pharma Inc)

Indication: For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia with a FMS-like tyrosine kinase 3 mutation.

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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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# Abbreviations

| | |
|---|---|
| AE | adverse event |
| AIC | Akaike Information Criteria |
| AML | acute myeloid leukemia |
| BIA | budget impact analysis |
| BIC | Bayesian Information Criteria |
| BSA | body surface area |
| BSC | best supportive care |
| CAD | Canadian Dollars |
| CGP | clinical guidance panel |
| EQ-5D | European Quality of Life Five Dimensions |
| FLAG-IDA | Fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin |
| FLT3 | FMS-like tyrosine kinase 3 |
| ICER | incremental cost-effectiveness ratio |
| HR | hazard ratio |
| HSCT | hematopoietic stem cell transplantation |
| KM | Kaplan-Meier |
| LDAC | low-dose cytarabine |
| LY | life year |
| MEC | mitoxantrone + etoposide + cytarabine |
| OS | overall survival |
| pCODR | CADTH pan-Canadian Oncology Drug Review |
| R/R | relapsed or refractory |
| SMR | Standardized mortality ratio |
| QALY | quality-adjusted life year |
| WTP | willingness-to-pay |

# Executive Summary

The executive summary is comprised of two tables (Table 1: Background; Table 2: Economic Evaluation) and a conclusion.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| Drug product | Gilteritinib (Xospata), 40 mg tablet. |
| Submitted price | Gilteritinib, 40 mg tablet: $325.00 |
| Indication | For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation.<br>A validated test is required to confirm the FLT3 mutation status of AML. |
| Health Canada approval status | NOC |
| Health Canada review pathway | Priority review |
| NOC date | Dec 23, 2019 |
| Reimbursement request | As per indication |
| Sponsor | Astellas Pharma Canada, Inc. |
| Submission history | Previously reviewed: No |

NOC = Notice of Compliance; AML = acute myeloid leukemia; FLT3 = FMS-like tyrosine kinase 3

## Table 2: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis.<br>Decision-tree followed by partitioned survival models. |
| **Target population** | Adult patients with relapsed or refractory acute myeloid leukemia with an FMS-like tyrosine kinase 3 mutation (aligned with reimbursement request). |
| **Treatment** | Gilteritinib |
| **Comparator** | Base case: Salvage chemotherapy (azacitidine, FLAG-IDA, MEC, and LDAC)<br>Scenario analyses: Best supportive care (BSC) and individual regimens (azacytidine only, FLAG-IDA only, MEC only, LDAC only) |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | Lifetime (41 years) |
| **Key data source** | ADMIRAL trial reporting overall survival and event-free survival without hematopoietic stem cell transplantation (HSCT). Medical literature reporting overall survival and event-free survival with HSCT. |
| **Submitted results for base case** | ICER = $114,800 per QALY (1.554 incremental QALYs; $178,423 incremental costs) |
| **Key limitations** | • The sponsor used a mixture of salvage therapy regimens to represent salvage chemotherapy in the base case, however the proportion of patients receiving each individual salvage regimen were based in the ADMIRAL trial and were not reflective of the clinical practice in Canada. Individual salvage regimen comparators were considered in scenario analysis, based on the inappropriate assumption that treatment efficacy of each individual regimen was the same as the salvage chemotherapy arm observed in the ADMIRAL trial. BSC was excluded from the base case analysis even though it was a relevant comparator, however it was included in a scenario analysis.<br>• The sponsor assumed that long-term survival was associated with mortality rates twice as high as that of the general population based on clinical expert opinion for a different product for FLT3-mutated AML that underwent reimbursement review in another country. Values from the literature suggest a 4 to 9-fold increase in mortality (compared to the general population). This suggests an overestimation in OS in the sponsor's analysis. Furthermore, the sponsor assumed that patients on maintenance gilteritinib post-HSCT would receive OS benefits, which was based on immature data with short follow-up. This assumption was deemed to be unrealistic and leads to further overestimation of OS favouring gilteritinib.<br>• Adjustment of treatment costs according to dose intensity underestimated costs of oral treatments, possibly favouring gilteritinib.<br>• Only grade 3 and 4 AEs that affected ≥5% of the patients were included in the sponsor's analyses. Some AEs considered clinically meaningful (such as cardiac toxicities, fatigue and vomiting) according to clinical experts and patient groups consulted by CADTH were excluded, possibly overestimating the benefits to gilteritinib. |
| **CADTH reanalysis results** | • CADTH reanalyses included: adding BSC as comparator, alternative salvage chemotherapy treatment distributions based on clinical expert feedback, alternative standardized mortality ratio (SMR) for long-term survivors based on the literature, exclusion of gilteritinib OS benefit post-HSCT, and revised dose intensity for oral treatments.<br>• BSC would be cost-effective if a decision-maker is willing to pay less than $98,720 for a QALY. Salvage chemotherapy is the optimal therapy if the willingness-to-pay threshold is at least $98,720 but less than $168,451 per QALY gained; and gilteritinib is the optimal therapy at a willingness-to-pay threshold of at least $168,451.<br>• A price reduction of approximately 40% and 90% would be required for gilteritinib 9to achieve an ICER of $100,000 and $50,000 per QALY, respectively. |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; FLAG-IDA = Fludarabine + cytarabine + granulocyte colony stimulating factor + idarubicin; HSCT = hematopoietic stem cell transplantation; LDAC = Low-dose cytarabine; LY = life-year; MEC = Mitoxantrone + etoposide + cytarabine; QALY= quality-adjusted life-year.

## Conclusions

CADTH undertook reanalyses to address some of the identified limitations, i.e., adding BSC as comparator, alternative salvage chemotherapy treatment distributions based on clinical expert feedback, alternative SMR for long-term survivors based on the literature, exclusion of post-HSCT gilteritinib benefit, and revised dose intensity for oral treatments.

Following CADTH reanalysis, BSC had the lowest cost and fewest QALYs followed by salvage chemotherapy and by gilteritinib. At a willingness-to-pay threshold of less than $98,720 per QALY BSC is the optimal therapy. Salvage chemotherapy is the optimal therapy if the willingness-to-pay threshold is at least $98,720 but less than $168,451 per QALY gained; and gilteritinib is the optimal therapy at a willingness-to-pay threshold of at least $168,451. A price reduction of approximately 40% and 90% for gilteritinib would be required to bring the ICER to $100,000, and $50,000 per QALY, respectively.

Some identified limitations could not be addressed by CADTH (e.g., missing relevant comparators such as midostaurin, the use of a fixed timepoint after which a proportion of patients undergo HSCT, the impact of different sequences of subsequent treatment, and impact of grade 1 and 2 AEs relevant to patients). Furthermore, the comparative-effectiveness of gilteritinib versus each individual salvage regimen (i.e., FLAG-IDA, MEC, azacitadine, LDAC) is unknown due to the lack of clinical efficacy data.

Based on the sponsor's submitted budget impact analysis, the total incremental cost is estimated to be [redacted] over the first 3 years. CADTH reanalysis suggests that the budget impact of introducing gilteritinib to the market was underestimated in the sponsor's results and estimated to be $47,750,562 over the first 3 years in CADTH reanalysis. *(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this economic information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

## Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

## Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 3: Detailed Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 4: CADTH Detailed Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 5: Detailed Information on the Submitted BIA

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

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