CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Sponsor)

Midostaurin (Rydapt) for Systemic Mastocytosis

April 2, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Rydapt (midostaurin) for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
Eligible Stakeholder Role	Manufacturer of the drug under review
Organization Providing Feedback	Novartis Pharmaceuticals Canada Inc.

** CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the initial recommendation:

☐ Agrees ☐ Agrees in part ☒ Disagrees

While we are disappointed in the recommendation for midostaurin for patients with advSM, we understand pERC's decision. Given the limitations of the clinical data in this ultra-rare disease, it is difficult within the existing recommendation framework to make an alternative recommendation. This poses a challenging situation because, as it has been noted by pERC, CGP, patient groups, and registered clinicians, there is an unmet need for effective treatment options in this very small group of patients.

We support the need for more clinical data with midostaurin for patients with advSM. We are committed to generate more data to address uncertainty in support of pERC's Next Step for Stakeholders regarding pERC's willingness to review new clinical data comparing midostaurin to currently available treatments in Canada.

The need for new mechanisms to support access treatments for patients with rare diseases has been described in the literature.[1] Many countries are modifying their access pathways for treatments for rare diseases because of the unique challenges that drugs for rare diseases pose.[1,2] For instance, the Scottish Medicines Consortium (SMC) has recently implemented a framework for drugs for ultra-rare diseases that allows the drug to be available to prescribers for a period of up to three years while further clinical effectiveness data are gathered.[3] After this period the company is asked to provide an updated submission for reassessment and SMC will make a decision on routine use of the medicine in NHS Scotland.[3]

We would like to kindly request that pERC would consider a scenario whereby midostaurin in advSM could be used as a demonstration of a risk sharing agreement with the public payers and Novartis to permit the collection of data for a subsequent submission to CADTH. We believe that midostaurin in advSM is a good candidate because:

1) Jurisdictions have indicated that there have been requests for access to midostaurin for advSM from their clinicians and patients;

2) Due to the ultra-rare nature of advSM, large comparative study would not be feasible;
3) Rydapt is recommended as a first line option for all advSM subtypes irrespective of KIT D816V mutation status by the NCCN guidelines;[4]
4) According to CGP and the clinician providing input in the submission, Rydapt should be the preferred first line option in all advSM cases "as it appears to be the most effective therapy and well tolerated" (initial clinical guidance report section 1.2.4 p21 and section 5 p36);[5]
5) The high ORR and long duration of response reported in study would most likely translate into OS benefit as stated by the CGP in the initial clinical guidance report (section 1.2.3 p15 and section 1.2.4 p19);[5]
6) This corroborated with outcomes of Canadian patients treated in the real world setting: Treatment with Rydapt was still ongoing for some patients after more than one (1), two (2) and even three (3) years since initiation of treatment.[6] In addition, 10-year follow-up results of study A2213 shows that ~40% and ~10% of patient were still alive 5 and 10 years after initiation of treatment respectively.[7] This is an important improvement given that advSM patients typically have a median survival of 3.5 years for ASM, 2 years for SM-AHN, and less than 6 months for MCL.[8]
7) Significant symptom improvement and decrease of transfusion dependency were also observed in study D2201.[9] This may have a positive impact on patients' quality of life as symptoms burden is their key concern.[5]

b) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ Agrees ☐ Agrees in part ☐ Disagrees

Note: Provisional algorithm was not included in this submission as it was not a requirement at the time of the submission.

c) Please provide editorial feedback on the initial recommendation to aid in clarity. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the stakeholder would support this initial recommendation proceeding to final recommendation ("early conversion"), which would occur two business days after the end of the feedback deadline date.

☐ Support conversion to final recommendation.

☒ Do not support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a final recommendation, please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the stakeholder during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a resubmission.

Additionally, if the eligible stakeholder supports early conversion to a final recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, the criteria for early conversion will be deemed to have not been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
4	SUMMARY OF pERC DELIBERATIONS	Paragraph: 8 Line: 6-7	As advSM is an extremely rare condition (~20 patients diagnosed per year in Canada), the budget impact at list price is expected to be low. In addition, as recognized by the CGP, treatment with Rydapt will not require additional resources compared to available cytoreductive therapies (chemotherapy units and chair time would not be required compared to cytoreductive therapies, and the frequency of clinic visits with Rydapt is typically not more than they would need otherwise).
9	ECONOMIC EVALUATION	Paragraph: 4 (Cost-utility estimates: Substantial uncertainty in clinical effectiveness estimates) Line: 20-23	The EGP re-analysis used an exponential function which is not the best fit according to AIC/BIC statistics. The choice of parametric function has a significant impact in the ICUR. Using the exponential function instead of log-normal function (best fit according to AIC/BIC statistics) has lead to an overestimation of the EGP estimate.

References

1. Nicod E et al. HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries. Health Policy. 2019 Feb;123(2):140-151.
2. Drugs for rare diseases: a review of national and international health technology assessment agencies and public payers' decision-making processes. Ottawa: CADTH; 2018. (Environmental scan; no. 77).
3. SMC (Scottish Medicine Consortium). Ultra-orphan medicines for extremely rare conditions. https://www.scottishmedicines.org.uk/how-we-decide/ultra-orphan-medicines-for-extremely-rare-conditions/
4. NCCN (National Comprehensive Cancer Network). (2019). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Systemic Mastocytosis. Version 2.2019
5. CADTH. pCODR Initial Clinical Guidance Report- - Midostaurin (Rydapt) for Systemic Mastocytosis. Jan 2020
6. Novartis Pharmaceutical Canada Inc. (2019). Midostaurin for Advanced Systemic Mastocytosis Managed Access Program. Data on file.
7. DeAngelo DJ, George TI, Linder A, et al. (2018). Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia. 32(2):470-478.
8. Lim KH et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol. 2009 Dec;84(12):790-4.
9. Gotlib J et al. (2016). Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 374(26):2530–41.

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pERC initial recommendation, including the provisional algorithm.

As part of the CADTH's pCODR review process, pERC makes an initial recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. The initial recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 business days within which to provide their feedback on the initial recommendation. It should be noted that the initial recommendation, including the provisional algorithm, may or may not change following a review of the feedback from stakeholders.

CADTH welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The stakeholder feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the initial recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part, or disagree with the initial recommendation, and to provide a rationale for their response. Please note that if a stakeholder agrees, agrees in part or disagrees with the initial recommendation, they can still support the recommendation proceeding to a final recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a final recommendation ("early conversion")?**

   An efficient review process is one of the key guiding principles for CADTH's pCODR process. If all eligible stakeholders support the initial recommendation proceeding to a final recommendation and that the criteria for early conversion as set out in the *Procedures for the CADTH Pan-Canadian Oncology Drug Review* are met, the final recommendation will be posted on the CADTH website two business days after the end of the feedback deadline date. This is called an "early conversion" of an initial recommendation to a final recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), including the provisional algorithm as part of the feasibility of adoption into the health system, the criteria for early conversion will be deemed to have **not** been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. If the substantive comments relate specifically to the provisional algorithm, it will be shared with CADTH's Provincial Advisory Group (PAG) for a reconsideration. Please note that if any one of the eligible stakeholders does not support the initial recommendation proceeding to a final recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the initial recommendation. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the initial recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with pERC, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with PAG.

The final recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit feedback on the initial recommendation:
   - The sponsor and/or the manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - CADTH's Provincial Advisory Group (PAG)

b) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - The sponsor and/or the manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Board of Directors of the Canadian Association of Provincial Cancer Agencies

- Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process.
- The template for providing stakeholder is located in section 3 of this document.
- The template must be completed in English. The stakeholder should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply.
- Feedback on the initial recommendation should not exceed three pages in length, using a minimum 11-point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.
- Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.
- References may be provided separately; however, these cannot be related to new evidence.
- *CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback must be disclosable and will be posted on the CADTH website.*
- The template must be filed with CADTH as a Microsoft Word document by the posted deadline.
- If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca