Draft Reimbursement Recommendation

Regorafenib

Reimbursement request: For the treatment of metastatic osteosarcoma in patients who have received at least 1 prior line of therapy.
Requester: Public drug programs
Draft recommendation: Reimburse with conditions

Summary

What is the Reimbursement Recommendation for Regorafenib?
The Formulary Management Expert Committee (FMEC) recommends that regorafenib be reimbursed for the treatment of patients with metastatic osteosarcoma who have received at least 1 prior line of therapy, provided certain conditions are met.

What are the Conditions for Reimbursement?

Regorafenib should only be reimbursed in patients for the treatment of metastatic osteosarcoma who have all the following: histologically confirmed osteosarcoma, received at least 1 prior line of therapy and have good performance status. A reduction in the price of regorafenib may be required.

Why did CDA-AMC Make This Recommendation?

FMEC reviewed two randomized controlled phase II trials (REGOBONE and SARC024) identified by CDA-AMC's systematic review of the literature. FMEC also considered input received from 1 clinician group (Pediatric Oncology Group of Ontario), two patient groups (Sarcoma Cancer Foundation of Canada and Advocacy for Canadian Childhood Oncology Research Network [Ac2orn]), and public drug programs.

FMEC concluded that there was uncertainty in the clinical value demonstrated by regorafenib; however, regorafenib was considered to fill a significant unmet clinical need arising from lack of treatments other than cytotoxic chemotherapy for metastatic osteosarcoma. The reimbursement conditions were further developed based on distinct social and ethical considerations, economic considerations, and impacts on health systems.

The reimbursement of regorafenib for the treatment of patients with metastatic osteosarcoma who have received and progressed on at least 1 prior line of therapy is expected to increase drug acquisition costs.

Therapeutic Landscape

What Is Metastatic Osteosarcoma?

Bone cancers are relatively rare, accounting for less than 1% of diagnosed cancers every year. Osteosarcoma is the most common primary bone tumour. The age at incidence of osteosarcoma diagnosis has two primary peaks, one in adolescence and early adulthood (15 to 20 years old) and a second, smaller peak in the seventh and eighth decades of life. Metastatic osteosarcoma has spread from the bone in which the cancer began to other parts of the body. Patients with metastatic osteosarcoma have very poor outcomes with little chance of cure, with less than 20% chance of survival at 5 years.

What Are the Current Treatment Options?

Treatment of osteosarcoma typically includes cytotoxic neoadjuvant and adjuvant chemotherapy in combination with surgical resection of the primary tumor. The current standard of care often used in the first line setting includes cisplatin and doxorubicin. In the second line, ifosfamide and etoposide are commonly used. When these options are exhausted, third-line treatments and beyond may include other chemotherapy combinations such as docetaxel and gemcitabine. However, the response rates to these treatments are generally low, and provide only temporary relief.

What Is the Treatment Under Review?

Regorafenib is an oral multitargeted tyrosine kinase inhibitor (TKI) which targets angiogenic, stromal, and oncogenic receptor tyrosine kinase. It is available as a 40 mg film coated tablet for oral administration.

Health Canada has approved regorafenib for colorectal, gastrointestinal and liver cancers. Regorafenib is used off label for osteosarcoma.

Why Did We Conduct This Review?

In most jurisdictions in Canada, patients with metastatic osteosarcoma only have access to cytotoxic chemotherapy as first or later lines of therapy. Targeted therapies especially TKIs are not available. TKIs like regorafenib have a unique mechanism of action that may fill an unmet need for treatments other than cytotoxic chemotherapy for patients with metastatic osteosarcoma. Regorafenib for metastatic osteosarcoma has been available to patients through the manufacturer's access program until its discontinuation in early 2025. This has prompted clinicians and the public drug programs to explore another avenue to access regorafenib in this setting.

Given the data protection for regorafenib has ended in 2021 and that there are two generics under review by Health Canada, this treatment is eligible for a non-sponsored reimbursement review as per the procedures for reimbursement reviews. At the request of the participating public drug programs, we reviewed the efficacy and safety of regorafenib in patients with metastatic osteosarcoma who have received at least one prior line of therapy.

Input From Community Partners

- Two patient groups **Sarcoma Cancer Foundation of Canada**, and **Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)** submitted input about the experience of living with sarcoma and the need for more treatment options to improve the patients and families' quality of life.

- One clinician group, the **Pediatric Oncology Group of Ontario** highlighted the current unmet needs for patients with metastatic osteosarcoma noting the lack of treatment options after first line which consists of further cytotoxic chemotherapy leaving many patients with no treatment options after first or second lines of therapy.

- **Public drug plans** inquired about the evidence for regorafenib to inform a recommendation on whether it should be reimbursed for metastatic osteosarcoma for patients who have had at least one prior line of therapy. The public drug plans outlined implementation questions related to treatment eligibility and potential costs.

► **Refer to the main report and the supplemental material document for this review.**

Person With Lived Experience

A young adult patient and her mother shared their journey with osteosarcoma. She described undergoing chemotherapy, and two surgeries to remove tumours, however, when not all tumors could be removed, her doctors introduced regorafenib. She valued how this treatment allowed her to regain a sense of normalcy—regrowing her hair, returning to school, traveling, and spending time with friends—without the constant nausea and fatigue of chemotherapy. While the drug kept her tumours stable and even shrank them for a time, painful calluses on her feet were a challenging side effect, but they were manageable. Her mother highlighted how this treatment reduced the burden on their family, and allowing for fewer hospital visits. After 18 months, the drug's effects waned, leading to a new treatment plan. She emphasized that Regorafenib allowed her to feel and live like a regular teenage girl for about a year and a half, and for that, she is extremely grateful.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person or caregiver might go through when facing this condition or treatment, helping to inform the committee's deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review.

Summary of Deliberation

FMEC discussed all domains of value of the deliberative framework prior to developing their recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, please refer to the Expert Committee Deliberation at Canada's Drug Agency document.

FMEC considered the following key discussion points, organized by the five domains of value.

Clinical Value

- **FMEC concluded that it is uncertain whether regorafenib demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.**

- Through reflection on the input from patient groups and insights shared by people with lived experience, FMEC members noted the following important patient values or perspectives:

    - The outcomes evaluated in the clinical trials including overall survival were important to patients. However, other important outcomes such as HRQoL, and overall symptom management were not assessed in either trial.

    - One patient group noted that having access to treatments that were more effective and more tolerable allowed the pediatric patients to pursue normal activities, attend school and achieve important milestones. According to the patient group and the people with lived experience, oral regorafenib offered a treatment with stability for the entire family.

    - One FMEC member noted that through the presentation by the PWLE, where she was able to experience life as a normal teenager for 1.5 years, the clinical value, specifically the improved quality of life, was realized, even though this was not captured in the reported clinical evidence.

- **FMEC** members highlighted the following points**:**

    - FMEC discussed the clinical evidence for regorafenib. In REGOBONE, the median PFS was 16.4 weeks (95% CI: 8.0 to 27.3) in the regorafenib group and 4.1 weeks (95% CI: 3.0 to 5.7) in the placebo group. At 12 weeks, the PFS was 62% and at 24 weeks, the PFS was 35% for the regorafenib group, while no patients were progression free at 12 weeks in the placebo group. In SARC024, the median PFS was 3.6 months (95% CI: 2.0 to 7.6 months) for regorafenib and 1.7 months (95% CI: 1.2 to 1.8 months) for placebo (HR: 0.42; 95% CI: 0.21 to 0.85; p-0.017). The PFS at 8 weeks and 16 weeks was 79.0% and 44.4% for patients receiving regorafenib, respectively, compared with 25.0% (Fisher's exact test p=0.001) and 10.0% (Fisher's exact test p = 0.027) for those receiving placebo.

    - FMEC discussed that although osteosarcoma is often diagnosed in children, recruiting pediatric patients is challenging in clinical trials. As such, there were no pediatric patients included in either of the trials considered by FMEC.

    - There were high crossover rates in both REGOBONE and SARC024 trials. The guest specialists highlighted that the cross overs were for ethical reasons, where the placebo groups with poor response rates were offered the treatment from the intervention arm. However, this crossover design

compromises the ability to assess the long-term efficacy of regorafenib on OS.

- FMEC discussed other clinical value of regorafenib including its more favourable safety profile. The guest specialists shared that clinicians have extensive experience with regorafenib in other disease settings. Regorafenib is better tolerated than other chemotherapeutic options, especially in older patients who may not tolerate dose-intense chemotherapy.

- FMEC also discussed that oral therapy may have the potential to address inequities in care that may be related to the need for access to specialized health care facilities.

Unmet Clinical Need

- **FMEC concluded that there is significant unmet clinical need arising from metastatic osteosarcoma despite available treatments.**

- Through reflection on the input from patient groups and insights shared by People with lived experience, FMEC members noted the following important patient values or perspectives:

  - Osteosarcoma is a debilitating cancer that can cause extreme pain, immobility and other symptoms affecting their activities of daily living. There is a need for additional treatment options that are more effective, tolerable and has the ability to alleviate the treatment burden, when compared to the current standard of care (e.g., chemotherapies)

- **FMEC** members highlighted the following points:

  - FMEC highlighted that bone tumours account for less than 1% of diagnosed cancers every year. Among all bone cancers, osteosarcoma is the most common type. In these patients who present with a primary lesion and an isolated pulmonary nodule, 5-year event-free survival is less than 20%.

  - FMEC also discussed that the second line therapy options in recurrent or refractory osteosarcoma are limited and provide low response rate and only temporary relief. These therapies include mostly chemotherapy options with high adverse effect burden and have significant impact on the patients' quality of life.

Distinct Social and Ethical Considerations

- **FMEC concluded that regorafenib would potentially address a significant nonclinical need arising from metastatic osteosarcoma despite available treatments. FMEC did not identify any measures that should be implemented to ensure that the use of regorafenib addresses relevant social and ethical implications.**

- **FMEC** members highlighted the following points**:**

- FMEC discussed the nonclinical needs that highlight the distinct social and ethical considerations. These include the ease of administration with an oral option as compared to an intravenous treatment, along with potential differences in the safety profiles.
- FMEC discussed that oral administration may provide benefit and allow administration at home. It may ease the need for travel to specialized treatment centers and result in reduced burden on patients and caregivers. Treatment with regorafenib may also have lower infectious disease related side effects or blood transfusion requirements.
- FMEC noted that the cost of oral medications is variable across jurisdictions and presents a concern for inequity. These treatments should be available for all patients regardless of where they reside within Canada.

Economic Considerations

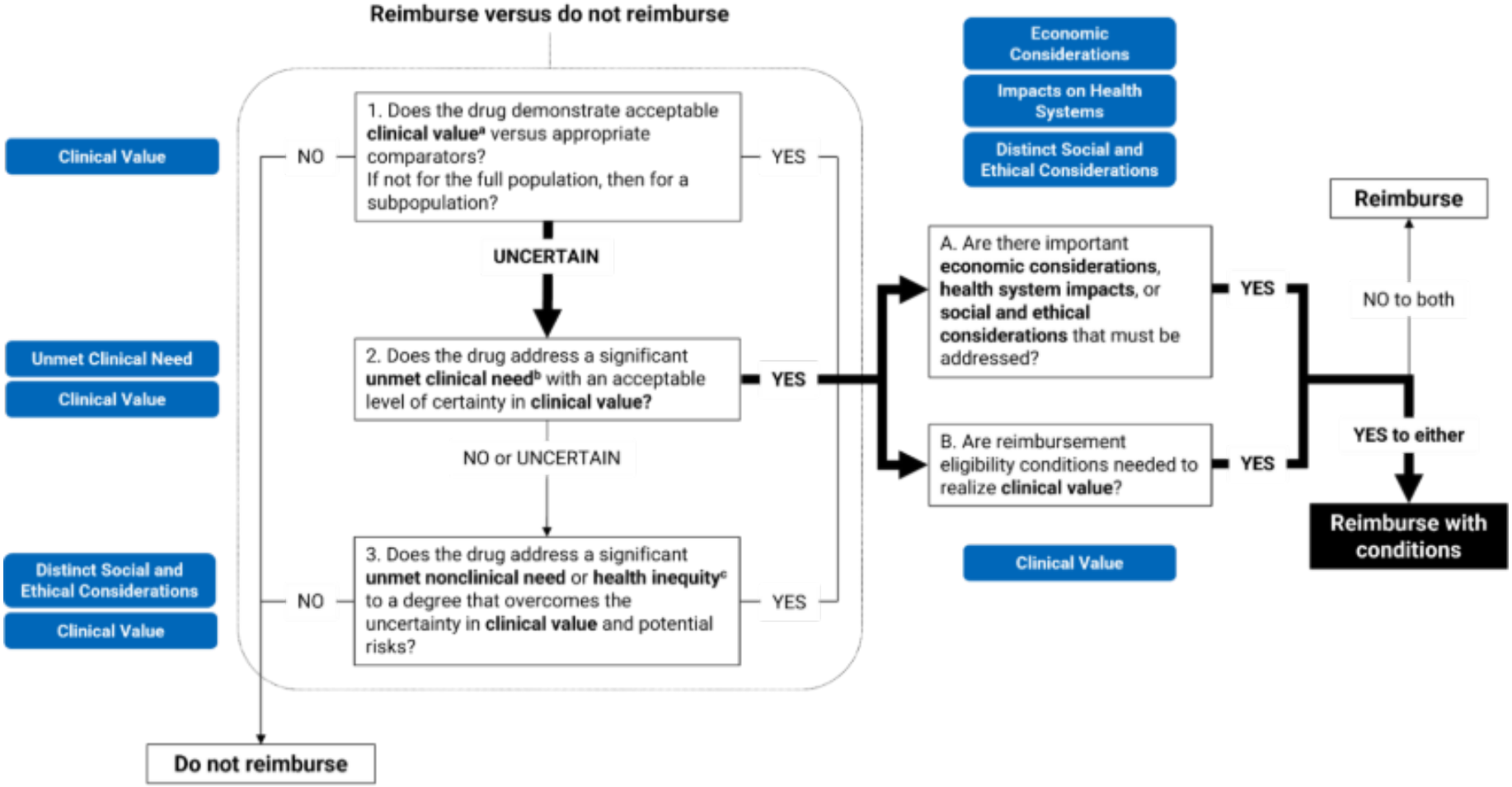
- **FMEC concluded that there are economic considerations that are important to address when implementing regorafenib.**
- **FMEC** members highlighted the following points:
  - The reimbursement of regorafenib for the treatment of adult and pediatric patients with metastatic osteosarcoma who have received and progressed on at least 1 prior line of therapy is expected to increase overall drug acquisition costs.
  - No evidence was identified regarding the cost-effectiveness of regorafenib relative to relevant comparators for the treatment of metastatic osteosarcoma in Canada, and therefore, estimates of cost-effectiveness were not available to the committee. FMEC discussed that a cost-effectiveness analysis would be valuable to fully inform the reimbursement recommendation. Additionally, FMEC emphasized that, in the absence of direct or indirect evidence, the comparative effectiveness of regorafenib remains unknown, further complicating the assessment of its overall value.
  - Given that regorafenib is associated with increased drug acquisition costs and unknown benefit relative to comparators, FMEC recommended a price reduction.
  - FMEC noted that the cost of regorafenib is expected to decrease following the expiration of its patent in August 2025, with 2 generic products currently under review by Health Canada. FMEC discussed that, under the pan-Canadian Pharmaceutical Alliance Tiered Pricing Framework, if a single generic product becomes available, its price is anticipated to decrease to $3,355 per 28-day cycle after 3 months of funding, making generic regorafenib less costly than comparator regimens at wholesale list prices. FMEC emphasized that if multiple generic products enter the market, the cost of generic regorafenib will be further reduced.

Impacts on Health Systems

- **FMEC did not identify considerations regarding impacts on health systems that are important to address when implementing regorafenib.**
- **FMEC** members highlighted the following points**:**
    - FMEC discussed that as an oral drug without additional requirements for testing, regorafenib eases the resources required for administration and potentially reduces resources required for the management of complications associated with other second line treatment options.

Figure 1: Recommendation Pathway

Alt-text: Flow chart indicating the steps used by the committee for this recommendation. The committee determined that it was uncertain whether the drug demonstrated acceptable clinical value versus appropriate comparators. However, the committee also determined that the drug addresses a significant unmet clinical need with an acceptable level of certainty in clinical value. Therefore, the committee recommended reimbursement of the drug for the patient population under consideration. After deliberating on economic considerations, impacts on health systems, distinct social and ethical considerations, and whether reimbursement conditions are needed to realize clinical value, the committee determined that reimbursement of the drug should be contingent upon 1 or more conditions being satisfied.



a Acceptable clinical value refers to at least comparable clinical value (if the drug is expected to be substitutive treatment) or added clinical value (if the drug is expected to be additive treatment) versus appropriate comparators.

b Significant unmet clinical need depends on all of the following: severity of the condition, availability of effective treatments, and challenges in evidence generation due to rarity of the condition or ethical issues.

c Unmet nonclinical need and health inequity are key components within the distinct and social ethical considerations domain of value.

Full Recommendation

With a vote of 8 to 0, FMEC recommends that regorafenib, for the treatment of metastatic osteosarcoma in patients who received at least 1 prior line of therapy, be reimbursed if the conditions presented in Table 1 are met.

Table 1: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Regorafenib may be initiated for the treatment of metastatic osteosarcoma in patients who meet all of the following: 1.1. Histologically confirmed osteosarcoma 1.2. Received at least 1 prior line of therapy 1.3. Have good performance status	The evidence from two RCTs (REGOBONE and SARC024) suggests a benefit of regorafenib for prolonging the time from treatment until disease worsening.	The trial's inclusion criteria included pediatric patients 10 years and older. However, there was no recruitment of patients reflecting this age group. As such, the clinical evidence is lacking for the pediatric population. The guest specialists consulted have expressed that regorafenib has become a standard of practice for this setting and for this pediatric patient population, given the experience of its use through the previously available patient assistance program.
Discontinuation and renewal		
2. Regorafenib should be discontinued if there is lack of clinical benefit or significant toxicity.	Consistent with clinical practice, patients in the SARC024 and REGOBONE trials discontinued treatment upon disease progression or significant toxicity.	Treatment should be continued while there are clinical benefits as per standard of care. FMEC has noted that in other common oncology indications, treatments are typically discontinued upon disease progression.
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of osteosarcoma.	This will ensure that appropriate treatment is prescribed for patients and adverse events are optimally managed.	

Reimbursement condition	Reason	Implementation guidance
Pricing		
4. A reduction in the price of regorafenib may be required.	The reimbursement of regorafenib for the treatment of adult and pediatric patients with metastatic osteosarcoma who have received and progressed on at least 1 prior line of therapy is expected to increase overall drug acquisition costs. No evidence was identified regarding the cost-effectiveness of regorafenib compared with ifosfamide plus etoposide, cyclophosphamide plus topotecan, and docetaxel plus gemcitabine for this indication in Canada. Therefore, estimates of cost-effectiveness were not available to the committee. A cost-effectiveness analysis would be needed to determine whether regorafenib is cost-effective. Furthermore, due to the lack of direct or indirect comparisons between regorafenib and relevant comparators, its comparative effectiveness remains unknown. Given that regorafenib is associated with increased drug acquisition costs and unknown clinical benefit relative to ifosfamide plus etoposide, cyclophosphamide plus topotecan, or docetaxel plus gemcitabine, price reductions may be required.	

Abbreviation:...

Feedback on Draft Recommendation

<to be updated after the feedback period>

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and two guest specialists from Alberta and Manitoba.

Meeting date: March 20, 2025

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the people with lived and living experience who presented directly to FMEC, and to the Canadian Sarcoma Research and Clinical Collaboration, particularly Natalia St Ville and Tamara Rowe.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.