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CADTH Reimbursement Recommendation

Ripretinib (Qinlock)

Indication: For the treatment of adult patients with advanced gastrointestinal stromal tumour who have received prior treatment with imatinib, sunitinib, and regorafenib

Sponsor: Medison Pharma Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Qinlock?

CADTH recommends that Qinlock be reimbursed by public drug plans for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Qinlock should only be covered to treat adult patients with GIST that has spread beyond the initial tumour site (advanced disease) and whose tumours have progressed while on treatment with imatinib, sunitinib, and regorafenib (which belong to the same drug class as Qinlock), or who could not take these drugs due to side effects.

What Are the Conditions for Reimbursement?

Qinlock should only be reimbursed if the drug is prescribed without any other anticancer drugs by a clinician with expertise in the treatment of GIST, and if the cost of Qinlock is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial showed that Qinlock delayed disease progression compared to placebo in patients with advanced GIST who were previously treated with other anticancer drugs for this condition. The results of this trial suggest that treatment with Qinlock improved survival and maintained quality of life.
- Qinlock meets patients' need for an effective fourth-line treatment for advanced GIST that delays disease progression and potentially prolongs survival. Qinlock also has an acceptable safety profile and comes as a convenient oral treatment.
- Based on public list prices, Qinlock is not considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) for the indicated population relative to best supportive care. A price reduction of at least 83% is required to ensure Qinlock is cost-effective at this threshold.
- Based on public list prices, the 3-year budget impact from the perspective of Canadian public drug plans is $34,454,158.

Additional Information

What Is GIST?

GISTs are rare cancers of the gastrointestinal tract which, as they grow and advance, may cause pain, bleeding, trouble swallowing, fatigue, vomiting, loss of appetite, and other gastrointestinal issues. Approximately 500 patients are diagnosed with GIST each year in Canada, and approximately 62 to 86 patients would be eligible for treatment with Qinlock each year.

Unmet Needs in GIST

Not all patients with advanced GIST respond to available treatments. Among those who do respond, responses are generally short-lived and become shorter with advancing lines of therapy. Currently, there are no standard treatment options for these patients for fourth line and beyond.

How Much Does Qinlock Cost?

Treatment with Qinlock is expected to cost approximately $18,171 per patient per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that ripretinib be reimbursed for the treatment of adult patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicenter, randomized, placebo-controlled trial (INVICTUS; N = 129) demonstrated that treatment with ripretinib resulted in added clinical benefit when compared with placebo in patients with GIST who had received prior treatment with imatinib, sunitinib, and regorafenib. The INVICTUS trial showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with ripretinib compared to placebo (hazard ratio [HR] = 0.15; 95% confidence interval [CI], 0.09 to 0.25; P < 0.0001). Because of failure of the statistical testing hierarchy and limitations owing to crossover and post-progression treatment, the overall survival (OS) benefit versus placebo could not be formally established but was suggestive of improved survival. Patients' health-related quality of life (HRQoL) appeared stable over time compared with placebo, although pERC was unable to draw definitive conclusions due to limitations of the evidence, namely absence of formal statistical testing, missing data, wide variation in estimates, and uncertainty regarding measurement properties. Changes in GIST symptoms were not directly assessed in the study. The safety profile of ripretinib was considered by patients and clinicians to be manageable and in line with that of other members of the drug class.

pERC agreed that there is a clear unmet need for effective treatments of advanced GIST in the fourth-line setting due to the absence of other viable options. Patients identified a need to reduce or control disease, improve survival, reduce cancer symptoms, enhance HRQoL, and avoid deleterious side effects. Given the totality of the evidence, pERC concluded that ripretinib meets some of these needs by delaying disease progression, resulting in potentially longer survival, while having an acceptable safety profile and offering a convenient oral option.

Using the sponsor-submitted price for ripretinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ripretinib was $242,365 per QALY compared with best supportive care. At this ICER, ripretinib is not cost-effective at a $50,000 per QALY WTP threshold for adult patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib. A reduction in price of at least 83% is required for ripretinib to be considered cost-effective at a $50,000 per QALY WTP threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with ripretinib should only be reimbursed when initiated in adults (≥ 18 years) with GIST who meet all of the following: 1.1. progression on or intolerance to imatinib, sunitinib, and regorafenib 1.2. adequate hematological and organ function.	Evidence from the INVICTUS trial demonstrated a clinical benefit in patients with GIST who received prior imatinib, sunitinib, and regorafenib and had adequate hematological function and organ function.	—
2. Patients should have good PS.	Evidence from the INVICTUS trial showed that patients with an ECOG PS of ≤ 2 benefited from ripretinib.	It is recognized that PS may be related to underlying disease and therefore for some patients, an improvement in status is expected after initiation of treatment. As such, clinicians could consider using ripretinib in patients with an ECOG PS of > 2 at their discretion.
3. Patients must not have any of the following: 3.1. active central nervous system metastases 3.2. clinically significant cardiac conditions or other comorbidities 3.3. gastrointestinal problems preventing the ingestion or absorption of oral medications.	These patients were excluded from the INVICTUS trial. No data were identified that demonstrate the efficacy and safety of ripretinib in these patients.	—
Renewal		
4. Reimbursement of ripretinib can be renewed in patients who demonstrate a response to treatment based on clinical assessment of PS, tolerance, and imaging. 4.1. Imaging should be performed every 2 to 4 months at the clinician's discretion.	According to the clinical experts consulted by CADTH, response to ripretinib treatment would be assessed by clinical evaluation in conjunction with imaging scans every 2 to 4 months.	—

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
5. Discontinuation would be based on a combination of clinical and radiological progression, significant adverse events potentially related to ripretinib, impact on HRQoL, and patient preference.	According to the clinical experts consulted by CADTH, ripretinib treatment would be discontinued following disease progression (either clinical symptomatic progression or radiographic progression), when significant adverse events occur (e.g., grade ≥ 3 elevated liver enzymes), when treatment intolerance persists despite dose reductions, or based on patient preference.	Clinicians may consider treating with ripretinib beyond progression if tolerated as there are no other treatment options in these patients and discontinuation may exacerbate disease progression and contribute to deterioration of symptoms and HRQoL. Limited data from the INVICTUS trial suggest that post-progression treatment may offer some degree of benefit.
Prescribing		
6. Ripretinib should initially be prescribed by a clinician with expertise in the treatment of GIST.	To ensure that ripretinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
7. Ripretinib should not be prescribed in combination with other anticancer drugs.	There is no data supporting the efficacy and safety of ripretinib when used in combination with other anticancer drugs.	—
Pricing		
8. A reduction in price	The ICER for ripretinib is $242,365 when compared with best supportive care. A price reduction of at least 83% would be required for ripretinib to be able to achieve an ICER of $50,000 per QALY compared to BSC.	—

BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; GIST = gastrointestinal stromal tumour; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; PS = performance status; QALY = quality-adjusted life-year.

Discussion Points

- pERC noted that patients with advanced, multi-resistant GIST in the fourth-line setting are rare and there is a lack of effective treatment options.
- pERC discussed the design and results of the INVICTUS trial, and agreed that best supportive care would be a relevant comparator in the fourth-line setting due to the absence of viable therapies. pERC also agreed that PFS is a meaningful end point in this patient population. pERC highlighted the significant and meaningful PFS benefit of ripretinib over placebo.
- pERC noted that the early failure of the statistical testing hierarchy of outcomes (i.e., when assessing overall response rate) meant that for some outcomes (OS and HRQoL), no robust conclusions could be drawn regarding the differences observed between the ripretinib and placebo groups. There was uncertainty in establishing the magnitude of the OS benefit because of the lack of statistical testing and confounding brought by patient crossover, post-progression treatment, and dose escalation. Nevertheless, pERC agreed that observed differences in OS suggest a positive effect of ripretinib on patient survival.

- CADTH was unable to address the uncertainty regarding the potential benefit of OS in the INVICTUS study. As a consequence of this and other limitations regarding treatment beyond progression and structural limitations of the model, CADTH's cost-effectiveness and price reduction estimates are likely biased in favour of ripretinib and remain highly uncertain.
- pERC acknowledged patients' concerns that coverage of orally administered cancer therapies differs across jurisdictions. Concerns were raised regarding the financial and administrative barriers in accessing oral cancer treatments such as ripretinib in some Canadian jurisdictions (specifically, in Ontario and the Atlantic provinces).

Background

GISTs are rare soft tissue sarcomas of the gastrointestinal tract. GISTs are typically characterized by primary gain-of-function mutations in CD117 (c-KIT), which account for 80% to 85% of GISTs, and platelet-derived growth factor alpha. Small and/or slow-growing GISTs may be clinically more benign, while tumours that grow significantly outward from the bowel wall can cause dysphagia, bleeding, abdominal pain and discomfort, fatigue, vomiting, loss of appetite, and other gastrointestinal issues. Both disease symptoms and the side effects of therapy severely impact HRQoL. At diagnosis, approximately half of patients with GISTs are eligible for potentially curative surgical resection. Among patients undergoing resection, disease will recur in about half of these patients within 5 years. Patients with advanced disease are transferred to the care of a medical oncologist for systemic therapy with palliative intent. According to the clinical experts consulted by CADTH for this review, in these patients, chemotherapy and radiotherapy are ineffective and the mainstay of therapy is sequential treatment with the tyrosine kinase inhibitors (TKIs) imatinib, sunitinib, and regorafenib. Responses to each line of therapy after imatinib are generally short-lived and development of resistance and disease progression occurs in most patients within months. After progression on third-line regorafenib, there are no standard therapy options beyond best supportive care and patient outcomes are unfavourable; further progression and mortality can be expected to occur within a few months.

Published data on the prevalence, incidence, and survival of advanced GIST in Canada are unavailable. Based on an estimated 500 GIST cases diagnosed per year in Canada, with 75% representing advanced GIST and assuming 80%, 70%, and 60% failure or progression rates on imatinib, sunitinib, and regorafenib, respectively, the sponsor estimated a target population of [redacted] patients with advanced GIST per year from 2023 to 2025 in Canada (outside of Quebec) who have received prior treatment with imatinib, sunitinib, and regorafenib and would be eligible for fourth-line ripretinib.

Ripretinib has been approved by Health Canada "for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with imatinib, sunitinib and regorafenib." Ripretinib is a TKI. It is available as 50 mg tablets and the dosage recommended in the product monograph is "150 mg (three 50 mg tablets) taken orally once daily."

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized controlled trial with an open-label period of active treatment in adult patients with unresectable advanced GIST who had progressed on or developed intolerance to imatinib, sunitinib, and regorafenib
- patients' perspectives gathered by 2 patient groups, the CanCertainty Coalition and the GIST Sarcoma Life Raft Group Canada (LRGC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with advanced GIST
- input from 1 clinician group, including 7 Canadian medical oncologists who treat patients with advanced GIST
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups submitted patient input for this review: the CanCertainty Coalition and the LRGC. CanCertainty raised concerns regarding the financial and administrative barriers in accessing cancer treatments such as ripretinib in some Canadian jurisdictions (specifically, in Ontario and the Atlantic provinces). Patients under the age of 65 who require take-home cancer treatment such as ripretinib and who do not have private or automatic public prescription drug coverage may incur significant deductibles or co-pays that come from their personal savings. These costs can become a financial burden and may lead to distress and hardship (this is estimated to affect approximately 5 patients per year).

In September and October 2021, LRGC conducted telephone interviews with 11 patients who have advanced GIST (5 patients living in Canada and 6 patients from the US) who had experience with ripretinib. All respondents were either initially or eventually diagnosed with metastatic GIST and many experienced delays in diagnosis due to nonspecific symptoms. Patients highlighted the negative impacts of advanced GIST on HRQoL, including symptoms of vomiting, abdominal pain and discomfort, bowel issues such as diarrhea, severe fatigue, black stools, and loss of appetite. Patients had received 1 to 4 lines of therapy before ripretinib and several recounted their rapid progression and sometimes severe side effects during treatment with prior TKIs. Most patients conveyed that ripretinib was generally more tolerable than other TKIs and had relatively minor side effects that included hair loss, cramping in body extremities, nausea, fatigue, hand and foot syndrome, foot calluses, and curly or kinky hair regrowth. More than half of patients reported improved HRQoL during ripretinib treatment compared with prior TKIs.

Patients with advanced GIST identified an unmet need for novel therapies that can stabilize or enhance HRQoL while effectively reducing disease progression for several years. In addition to improved survival, patients desired access to new drugs with improved toxicity profiles, longer-term effectiveness, and the ability to target specific GIST mutations.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

Two clinical experts with expertise in the diagnosis and management of patients with advanced GIST were consulted for this review. According to the clinical experts, not all patients with metastatic GIST respond to available treatments, such as TKIs, and responses are generally short-lived, especially in later lines of therapy. Following exhaustion of available TKIs (imatinib, sunitinib, and regorafenib), there are no standard treatment options available in Canada, and additional lines of therapy are required to fulfill the unmet needs of these patients. According to the clinical experts, the goals of fourth-line treatment of advanced GIST following progression or intolerance to imatinib, sunitinib, and regorafenib are prolonging survival, delaying disease progression, and palliation of symptom or prevention of new symptom development. The clinical experts stated that based on currently available evidence, ripretinib would be used for fourth-line monotherapy after progression on or intolerance to imatinib, sunitinib, and regorafenib and would not result in a treatment paradigm shift, but rather would provide an additional option for later-line therapy in patients with no other options. According to the clinical experts, there are no established biomarkers of response to ripretinib and all patients with advanced GIST who experienced progression or intolerance on imatinib, sunitinib, and regorafenib with adequate performance status (PS), organ function, and hematological function would be candidates for ripretinib irrespective of tumour mutational status. Patients with poor PS, limited organ and hematological function, significant comorbidities (especially cardiac problems), central nervous system metastases, and problems ingesting or absorbing oral medications would be least suitable for ripretinib treatment.

The clinical experts consulted by CADTH stated that treatment with ripretinib would be initiated either immediately following disease progression on third- line treatment (regorafenib) or after symptoms worsen following discontinuation of third-line treatment. According to the clinical experts, response to ripretinib treatment would be assessed by clinical evaluation in conjunction with imaging scans every 2 to 4 months. Clinically meaningful responses to therapy would be reflected by restricted tumour growth, prolongation of OS and PFS, maintained or improved HRQoL, and stabilization or reduction of symptom severity. Treatment would be discontinued following disease progression, or with significant adverse events, or when treatment intolerance persists despite dose reductions, or based on patient preference. The clinical experts additionally noted the convenience of ripretinib as an oral drug that can be self-administered at home in this advanced disease setting.

Clinician Group Input

One group of 7 Canadian medical oncologists who treat patients with advanced GIST, some of whom are medical advisors to LRGC, provided input for this review. No major contrary views were presented. The clinicians echoed the absence of fourth-line treatment options for patients after available TKIs (imatinib, sunitinib, and regorafenib) have been exhausted and the poor outcomes in these patients. Minor discrepancies were noted between clinician

and clinician group input in the frequency of response assessment by imaging scans (2 to 4 months versus 3 to 4 months, respectively), potentially due to jurisdictional variation.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation Issues	Response
Relevant comparators	
PAG noted that BSC is a relevant comparator in patients with GIST who have progressed on imatinib, sunitinib, and regorafenib.	pERC agrees that BSC is a relevant comparator.
Considerations for continuation or renewal of therapy	
Patients in the INVICTUS study received tumour assessments (via CT or MRI scans) every cycle for the first 3 cycles, then every other cycle starting at cycle 4. In clinical practice, what is the most appropriate frequency or modality to determine treatment response?	pERC agreed that in Canadian clinical practice, imaging scans would be performed every 2 to 4 months rather than every cycle. CT scan would be used more commonly than MRI scan.
Considerations for discontinuation of therapy	
At the time of disease progression in the INVICTUS trial, patients could either escalate their dosage to 150 mg ripretinib orally twice daily, continue 150 mg orally once daily if there is continued clinical benefit, or discontinue therapy. What would be appropriate discontinuation criteria for ripretinib?	pERC agreed that clinicians may consider treating with ripretinib beyond progression if tolerated as there are no other treatment options in these patients and discontinuation may exacerbate disease progression and contribute to deterioration of symptoms and HRQoL. Limited data from INVICTUS suggest that post-progression treatment may offer some degree of benefit.
Considerations for prescribing of therapy	
PAG noted that the usual dose of ripretinib is 150 mg (3 50 mg tablets) orally once daily. Lexicomp drug information database cautions not to use ripretinib 1 week before elective surgery and not for at least 2 weeks post-surgery or until adequate wound healing.	pERC acknowledges dosing considerations for ripretinib.
Care provision issues	
PAG noted that as per the product monograph, ripretinib tablets are 50 mg and supplied in a bottle of 90 tablets. It is recommended to "Store in the original container at room temperature." In the event of dosage reduction, this storage restriction (original packaging) could lead to dispensing issues. The original container is to maintain the desiccant provided. In the US, there is a restricted dispensing program that does not appear in the Health Canada monograph.	pERC acknowledges potential issues with dispensing ripretinib tablets.
PAG noted that ripretinib has multiple potential drug-drug, drug-food (e.g., grapefruit), and drug-herb interactions requiring assessment and potential intervention.	pERC agreed that pharmacists would be important to identify such drug interactions.

BSC = best supportive care; HRQoL = health-related quality of life; PAG = Provincial Advisory Group.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

INVICTUS was a phase III, double-blind, multicenter, randomized placebo-controlled trial (N = 129) with an open-label period of active treatment. The primary objective of the study was to assess the efficacy of ripretinib in prolonging PFS per blinded independent central review (BICR) in patients with advanced GIST who had received prior anticancer therapies, including imatinib, sunitinib, and regorafenib. Secondary objectives included comparing objective response rate (ORR) per BICR (hierarchically tested), OS (hierarchically tested), patient-reported changes in disease symptoms and HRQoL from baseline to the start of cycle 2 (hierarchically tested), and other efficacy outcomes, including duration of response between the ripretinib and placebo arms. Patients were enrolled at 29 sites in 12 countries (one site in Toronto, Canada) and randomized to double-blind treatment with either ripretinib 150 mg orally once daily plus best supportive care or placebo orally once daily plus best supportive care. Following initial objective disease progression per BICR, patients and investigators were unblinded to treatment allocation, and patients could choose to receive open-label ripretinib either at the same dose (150 mg orally once daily) or to dose escalate to open-label ripretinib 150 mg orally twice daily. Following treatment discontinuation, patients entered survival follow-up.

Adult patients with unresectable advanced GIST who had progressed on or developed intolerance to imatinib, sunitinib, and regorafenib were eligible for the study if they had an Eastern Cooperative Oncology Group (ECOG) PS 0, 1, or 2 and did not have active central nervous system metastases, clinically significant cardiac conditions or other comorbidities, or gastrointestinal problems preventing the ingestion or absorption of oral medications. The mean age of participants was approximately 60 years, approximately 57% were male, approximately 75% were White, and approximately 47% were enrolled at sites in the US. The most common tumour site was gastric (45.0%) and the most common location of primary tumour mutations was KIT exon 11 (58.1%). Approximately 60% of patients had received 3 prior lines of therapy, while approximately 40% had received 4 or more prior lines of therapy. Baseline demographic and disease characteristics were generally well balanced between study arms, apart from minor imbalances of potential prognostic relevance in age, ECOG PS, and gastric tumour site. The clinical experts consulted by CADTH for this review did not feel that any of these imbalances would likely impact the study results.

Efficacy Results

Importantly, the OS analysis in the INVICTUS study did not account for crossover from the placebo group to the ripretinib group following initial objective disease progression, post-progression ripretinib treatment, or post-progression dose escalation to the non-Health Canada–approved dosage of 150 mg orally twice daily. At the time of the primary analysis (database lock on May 31, 2019), median OS was 28.6 weeks (95% CI, 17.9 weeks to 50.4 weeks) in patients originally randomized to the placebo arm and 65.6 weeks (95% CI, 53.6 weeks to 65.6 weeks) in patients originally randomized to the ripretinib arm. The HR for OS comparing ripretinib to placebo was 0.36 (95% CI, 0.21 to 0.62). A post hoc subgroup analysis of OS by combined treatment assignment in both the double-blind and open-label periods showed the following results: (1) double-blind placebo, no crossover, median OS 7.9 weeks (95% CI, 3.7 weeks to 19.6 weeks); (2) double-blind placebo with crossover to open-label

ripretinib 150 mg once daily, median OS 30.1 weeks (95% CI, 12.4 weeks to not calculable); (3) [redacted] and (4) [redacted]. During double-blind treatment, no objective tumour responses occurred in the placebo arm while the ORR at the time of the primary analysis was 9.4% (95% CI, 4.2% to 17.7%) in the ripretinib arm (P = 0.0504). Among patients responding to ripretinib, median duration of response was not estimable at the time of the primary analysis (May 31, 2019, data cut off) but was 14.5 months (95% CI, 3.7 months to not estimable) at the more recent data cut off of January 15, 2021. At the time of the primary analysis, median PFS during double-blind treatment was 4.1 weeks (95% CI, 4.0 weeks to 7.3 weeks) in the placebo arm and 27.6 weeks (95% CI, 20.0 weeks to 29.9 weeks) in the ripretinib arm (P < 0.0001). The HR for PFS comparing ripretinib to placebo was 0.15 (95% CI, 0.09 to 0.25). OS, ORR, and PFS results for the most recent data cut off (January 15, 2021) were similar or numerically higher in favour of ripretinib. The results of the primary PFS analysis were statistically and clinically significant according to the clinical experts consulted by CADTH for this review. Comparisons of OS and ORR (despite their descriptive nature and nonstatistical significance, respectively, and despite the complexities of the OS analysis) were viewed by the clinical experts as being supportive of the PFS findings, and were judged to be potentially clinically important given that the population is affected by advanced disease and has no other available treatment options.

HRQoL indicators (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item [EORTC QLQ-C30] role and physical function, EQ-5D 5-Level [EQ-5D-5L] usual activities and pain or discomfort, EQ-5D-5L utility index scores, and EQ-visual analogue scale [VAS]) were similar at baseline in the ripretinib and placebo arms. Interpretation of changes from baseline to cycle 2 day 1 was limited by several factors (refer to the Critical Appraisal section).

Harms Results

Adverse events (AEs) occurred in most patients treated with placebo (97.7%) and ripretinib (98.8%). Serious AEs occurred in more patients who received placebo (44.2%) than in those who received ripretinib (30.6%). Withdrawals due to AEs occurred in 11.6% of patients treated with placebo and 8.2% of patients treated with ripretinib. Deaths were more frequent among patients who were treated with placebo (23.3%) than among those who were treated with ripretinib (5.9%), primarily due to disease progression.

Among protocol-specified AEs of special interest, squamous cell carcinoma of the skin did not occur in patients who received placebo, but did occur in 2 patients (2.4%) who received ripretinib. Actinic keratosis occurred in 1 patient (2.3%) who received placebo and 5 patients (5.9%) who received ripretinib. All notable harms specified in the CADTH review protocol occurred more frequently in patients who received ripretinib than in those who received placebo: cardiac dysfunction, cardiac ischemic events, hypertension, cutaneous malignancies, palmar-plantar erythrodysesthesia syndrome, arthralgia, myalgia, and increased bilirubin. The most common AEs by preferred term were peripheral edema (ripretinib versus placebo = 16.5% versus 7.0%), hypertension (ripretinib versus placebo = 14.1% versus 4.7%), palmar-plantar erythrodysesthesia syndrome (ripretinib versus placebo = 21.2% versus 0%), arthralgia (ripretinib versus placebo = 17.6% versus 4.7%), myalgia (ripretinib versus placebo = 31.8% versus 11.6%), and increased bilirubin (ripretinib versus placebo = 16.5% versus 0%).

Critical Appraisal

The major limitation of the INVICTUS trial was its small size and associated uncertainty, although this was expected for a study of a rare disease. The clinical experts consulted by CADTH for this review did not think that the minor baseline differences between arms (in favour of ripretinib) in age, ECOG PS, and tumour site would affect the study results. Because of elective crossover of patients from double-blind placebo to open-label ripretinib 150 mg orally once daily and the elective intra-patient post-progression dose escalation to 150 mg orally twice daily (a non-Health Canada–approved dose), the relative impacts of ripretinib versus placebo treatment, pre- versus post-progression treatment, and ripretinib dose on OS could not be ascertained from the study data. Early failure of the statistical hierarchy at the time of the primary analysis precluded testing of OS and HRQoL differences between arms. Analyses of HRQoL outcomes were further limited by missing data, and uncertainty regarding the measurement properties or minimal important differences of the instruments used in patients with GIST. Changes in GIST symptoms were not directly assessed in the study.

The demographic and disease characteristics of the INVICTUS study population were considered broadly reflective of the Canadian patient population with advanced GIST who would be eligible for ripretinib, according to the clinical experts consulted by CADTH for this review. There were no major generalizability concerns to smaller subgroups (e.g., tumour mutational status); however, the descriptive OS results should not be generalized to clinical practice due to the inability to account for patient crossover from placebo to ripretinib, post-progression open-label treatment, and dose escalation during open-label treatment to 150 mg orally twice daily. The impact of crossover from placebo to open-label ripretinib would be expected to bias OS comparisons against ripretinib, while the impacts of post-progression treatment and intra-patient dose escalation were uncertain.

Indirect Comparisons

No indirect evidence was identified for this review.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib
Treatment	Ripretinib
Submitted price	Ripretinib, 50 mg tablet: $216.32

Component	Description
Treatment cost	The cost for ripretinib is $18,171 per 28 days
Comparator	BSC (basket of medications for managing symptoms of GIST related to pain, GI support, anemia, nutritional support, sleep, emotional support, and infections)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (16 years)
Key data source	Clinical efficacy was modelled using OS and PFS observed in the INVICTUS trial. Health state utility values were estimated using EQ-5D 5-Level data collected from the same trial.
Key limitations	• Due to limitations with the trial evidence, CADTH's clinical review of the INVICTUS trial could not definitively state whether treatment with ripretinib improved OS. The sponsor's pharmacoeconomic model relies heavily on the OS data, and its estimates of incremental effectiveness are therefore highly uncertain. This data were extrapolated far beyond the length of the submitted OS data (33 months), which adds additional uncertainty. • Based on feedback from the clinical experts, the sponsor's choice of parametric survival function overestimates the survival of patients with advanced GIST. • The magnitude of comparative clinical effectiveness of ripretinib relative to BSC is uncertain. The sponsor's model results suggested that patients receiving ripretinib lived longer following disease progression than those receiving BSC, which was not supported by post-progression survival evidence from INVICTUS. Estimates of incremental effectiveness may be biased in favour of ripretinib. • In the sponsor's base case, patients received a fixed dose of ripretinib, and discontinued ripretinib at the time of disease progression. The sponsor did not adjust for the existence of dose escalation or post-progression treatment within the INVICTUS trial data, which confers an unknown clinical benefit and biases estimates of cost-effectiveness in favour of ripretinib. • The clinical experts consulted by CADTH suggested that the sponsor's base case estimates of health state utility were unrealistic. Health state utility following progression was not meaningfully different from pre-progression utility, both of which were unrealistically high based on clinical expert feedback. QALYs were thereby overestimated in favour of ripretinib. • The sponsor's use of RDI may underestimate drug costs and does not account for other factors that influence dosing such as dose delays, dose reductions, or dose escalations.
CADTH reanalysis results	• CADTH's base case considered a Weibull parametric function to extrapolate OS, adjustment for treatment beyond disease progression in the ripretinib arm, health state utility values that were deemed to be more clinically feasible, and a revised RDI of 100%. • Based on the CADTH base case, ripretinib is associated with an ICER of $242,365 per QALY and the probability of cost-effectiveness at a WTP threshold of $50,000 per QALY is 0%. A price reduction of 83% is necessary to achieve cost-effectiveness at this threshold.

BSC = best supportive care; GI = gastrointestinal; GIST = gastrointestinal stromal tumour; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RDI = relative dose intensity; WTP = willingness to pay.

Budget Impact

CADTH identified key limitations with the sponsor's analysis; namely, that the market shares for ripretinib were underestimated and that median PFS was used to calculate drug acquisition costs rather than the mean treatment duration. CADTH reanalysis increased the market shares for ripretinib and applied the mean treatment duration to calculate costs. In the CADTH base case, the budget impact of ripretinib is expected to be $9,967,633 in year 1, $12,186,842 in year 2, and $12,299,683 in year 3, with a 3-year total budget impact of

$34,454,158. CADTH found the budget impact of ripretinib to be sensitive to market shares and length of treatment duration.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: March 9, 2022

Regrets: One expert committee member did not attend.

Conflicts of interest: None