Reimbursement Review

Regorafenib (N/A)

Draft Supplemental Material

Requester: Public drug programs

Therapeutic area: Osteosarcoma

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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

Background Appendices

Appendix 1

Table 1. Key Characteristics of Regorafenib and comparators

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
Regorafenib	Multikinase inhibitor. Blocks tyrosine kinases that are very active in angiogenesis, cancer development and growth, and maintenance of the tumor microenvironment	None (no HC indication for osteosarcoma)	160 mg/day, for 21 of 28 days, oral tablets	Hand-foot syndrome Hypertension Mucositis Rash Cytopenia
Comparators				
Ifosfamide +/- etoposide	Ifosfamide Antineoplastinc agent An alkylating and immunosuppressive agent used in chemotherapy for the treatment of cancers. etoposide Antineoplastic agent Cytostatic action which prevents the cells from entering mitosis or destroys them in the pre-mitotic phase.	Ifosfamide Soft tissue sarcoma, pancreatic carcinoma, cervical carcinoma etoposide Small cell carcinoma of the lung, malignant lymphoma, non-small cell carcinoma of the lung, testicular malignancies	Intravenous	Various systemic toxicities, Nausea and vomiting, secondary tumours
Cyclophosphamide and topotecan	Alkylating agent Prevents cell division by cross linking DNA and RNA strands Topotecan	Cyclophosphamide Malignant lymphomas, multiple myeloma, leukemias, solid malignancies (neuroblastoma, breast carcinoma, retinoblastoma)	Intravenous	Various systemic toxicities, Nausea and vomiting, secondary tumours

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
	Antineoplastic agent Topoisomerase 1 inhibitor. Works by blocking DNA topoisomerase 1.	<u>Topotecan</u> Metastatic carcinoma of the ovary, sensitive small cell lung cancer		
Gemcitabine +/- docetaxel	<u>Gemcitabine</u> Antimetabolite nucleoside analog, exerts its antiproliferative action after tumoral conversion into active triphosphorylated nucleotides interfering with DNA synthesis and targeting ribonucleotide reductase. <u>Docetaxel</u>: Taxane Interferes with microtubules, blocks cell growth by stopping mitosis.	<u>Gemcitabine</u> adenocarcinoma of the pancreas, non-small cell lung cancer (NSCLC), transitional cell carcinoma (TCC) of the bladder, breast cancer <u>Docetaxel</u>: Breast cancer, non small cell lung cancer (NSCLC), ovarian cancer, prostate cancer, squamous cell carcinoma of the head and neck	Intravenous	Various systemic toxicities

[a] Health Canada–approved indication.

Clinical Review Appendices

Appendix 2: Methods of the Clinical Review

For the systematic review, we included studies that adhered to the a priori eligibility criteria detailed in Table 2 in the main review report. We also included long-term extension (LTE) studies of included RCTs, regardless of whether there was a comparison group. We included indirect treatment comparisons (ITCs) that adhered to the eligibility criteria, except for the study design criteria. Studies addressing gaps were those identified by the review team and/or clinical experts that did not meet the eligibility criteria but were considered to address important gaps in the Systematic Review evidence.

Search Strategy

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were regorafenib and osteosarcoma. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language.

The initial search was completed on October 30, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) on March 20, 2025.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials.

A focused literature search for indirect treatment comparisons (ITCs) dealing with regorafenib and osteosarcoma was run in MEDLINE on October 31, 2024. The search was limited to indirect treatment comparisons.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: October 30, 2024

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits: None

Table 2: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

1. (regorafenib* or Resihance or Stivarga or Rezitix or Regocent or Regonat or Stivar or bay-734506 or bay734506 or bay-73-4506 or bay73-4506 or ro-7069680 or ro7069680 or 24T2A1DOYB).ti,ab,kf,ot,hw,rn,nm.
2. *regorafenib/ or (regorafenib* or Resihance or Stivarga or Rezitix or Regocent or Regonat or Stivar or bay-734506 or bay734506 or bay-73-4506 or bay73-4506 or ro-7069680 or ro7069680).ti,ab,kf,dq.
3. exp bone neoplasms/ or exp neoplasms, bone tissue/ or exp sarcoma/ or (bone* or sarcoma* or osteosarcoma* or osteochondrosarcoma* or osteogenic* or osteoid* or ewing*).ti,ab,kf.
4. 1 and 3
5. exp bone tumor/ or exp sarcoma/ or (bone* or sarcoma* or osteosarcoma* or osteochondrosarcoma* or osteogenic* or osteoid* or ewing*).ti,ab,kf.
6. 2 and 5
7. 4 use medall
8. 6 use oemezd
9. 7 or 8
10. remove duplicates from 9

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

[Keyword search terms: (regorafenib OR Resihance OR Stivarga OR Rezitix OR Regocent OR Regonat OR Stivar OR "BAY-734506" OR BAY734506 OR "BAY-73-4506" OR "BAY73-4506" OR "RO-7069680" OR RO7069680 OR 24T2A1DOYB) AND (osteosarcoma OR sarcoma OR sarcomas OR bone OR bones)]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

[Keyword search terms: (regorafenib OR Resihance OR Stivarga OR Rezitix OR Regocent OR Regonat OR Stivar OR "BAY-734506" OR BAY734506 OR "BAY-73-4506" OR "BAY73-4506" OR "RO-7069680" OR RO7069680 OR 24T2A1DOYB) AND (osteosarcoma OR sarcoma OR sarcomas OR bone OR bones)]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Keyword search terms: regorafenib or Stivarga or BAY 73-4506 or BAY734506 OR BAY73-4506]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Keyword search terms: (regorafenib OR Resihance OR Stivarga OR Rezitix OR Regocent OR Regonat OR Stivar OR "BAY-734506" OR BAY734506 OR "BAY-73-4506" OR "BAY73-4506" OR "RO-7069680" OR RO7069680 OR 24T2A1DOYB) AND (osteosarcoma OR sarcoma OR sarcomas OR bone OR bones)]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Keyword search terms: regorafenib, Resihance, Stivarga, Rezitix, Regocent, Regonat, Stivar, BAY-734506, BAY734506, BAY-73-4506, BAY73-4506, RO-7069680, RO7069680, 24T2A1DOYB]

Grey Literature

Search dates: October 17, 2024 – October 24, 2024

Keywords: regorafenib, Stivarga, Rezitix, Regocent, Regonat, Stivar, osteosarcoma, bone sarcoma, bone cancer

Limits: none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search
- Open Access Journals

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical expert(s), and patient and clinician groups, with input from a methodologist.

Appendix 3: Cost Comparison Table

The comparators presented in Table 1 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on regimen monographs from Cancer Care Ontario[1] and validated by clinical experts. If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on wholesale list prices from the IQVIA Delta PA database.[2]

The recommended dose of regorafenib is 160 mg daily for 3 weeks on and 1 week off in 28-day cycles (Table 1). At $72.62 per 40 mg tablet, the treatment acquisition cost of regorafenib is $217.86 daily, or $6,100 per patient per 28-day cycle. The incremental cost of regorafenib compared with ifosfamide plus etoposide, cyclophosphamide plus topotecan, and docetaxel plus gemcitabine is $2,016, $1,681, and $2,677 per patient per 28 days, respectively. Results may differ by jurisdiction depending on individual list prices for the drug under review compared to those presented in Table 1.

Table 1: CDA-AMC Cost Comparison Table for patients with metastatic osteosarcoma who have received and progressed on at least 1 prior line of therapy

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cost ($)
Regorafenib (Stivarga)	40 mg	Tablet	72.6200	160 mg daily for three weeks on, one week off per 28-day cycle, as long as treatment benefit is observed or until unacceptable toxicity[a]	217.86	6,100
Ifosfamide plus etoposide						
Ifosfamide (Ifex)	1000 mg 3000 mg	Powder for injection	154.2067 462.6201	1800 mg/m^2 Days 1 to 5 every 21 days until progression or unacceptable toxicity	110.15	3,084
Etoposide (generics)	100 mg 200 mg 500 mg 1000 mg	20 mg/mL concentrated solution for IV injection	75.0000 150.0000 375.0000 750.0000	100 mg/m^2 Days 1 to 5 every 21 days until progression or unacceptable toxicity	35.71	1,000
Ifosfamide plus etoposide					145.86	4,084
Cyclophosphamide plus topotecan						
Cyclophosphamide (generics)	500 mg 1000 mg 2000 mg	20 mg/mL powder for IV injection	107.8100 195.4200 359.4000	250 mg/m^2 on Days 1 to 5, every 21 days until progression or unacceptable toxicity	25.67	719
Topotecan (generics)	4 mg	1 mg/mL powder for IV injection	555.0000	0.75 mg/m^2 on Days 1 to 5, every 21 days until progression or unacceptable toxicity	132.14	3,700
Cyclophosphamide plus topotecan					157.81	4,419
Docetaxel plus Gemcitabine						

Docetaxel (generics)	80 mg 160 mg	20 mg/mL concentrated solution for IV infusion	499.0000 990.0000	100 mg/m^2 Day 8 every 21 days until progression or unacceptable toxicity	70.81	1,985
Gemcitabine	1000 mg 2000 mg	40 mg/mL	270.0000 540.0000	900 mg/m^2 Days 1 and 8 every 21 days	51.43	1,440
Docetaxel plus Gemcitabine					122.24	3,423

Note: All prices are from IQVIA DeltaPA (December 2024),[2] unless otherwise indicated, and do not include dispensing fees. Costs assume a patient with a body surface area of 1.8 m^2. All doses are from the Cancer Care Ontario Regimen Formulary Database[1] for the palliative treatment of sarcoma unless otherwise indicated. Costs include wastage of excess medications in vials, where applicable.

[a] As dosed in the SARC024 trial,[3] where patient eligibility was 10 years of age or older with a body surface area 0.65m^2 or greater (note: no patients under 18 were recruited). In practice, according to clinical expert input patients may start at a lower dose (e.g. 80 mg) and escalate up to 160 mg daily to improve tolerability and adherence. Regorafenib tablets come in 28-tablet bottles and should be discarded 7 weeks after opening.[4] At the usual dose of 160 mg daily, a bottle lasts one week. Should patients need to temporarily suspend dosing and resume at a lower dose, wastage may occur.

1. Cancer Care Ontario. Funded evidence-informed regimens. 2024. Accessed December 14, 2024. https://www.cancercareontario.ca/en/drugformulary/regimens
2. IQVIA. *DeltaPA*. 2024. Accessed December 14, 2024. https://www.iqvia.com/
3. Davis LE, Bolejack V, Ryan CW, et al. Randomized double-blind phase II study of regorafenib in patients with metastatic osteosarcoma. *J Clin Oncol*. 2019;37(16):1424-1431. doi:10.1200/JCO.18.02374
4. Bayer Inc. *Stivarga (regorafenib): 40 mg tablets [product monograph]*. March 9, 2020. Accessed December 28, 2024. https://pdf.hres.ca/dpd_pm/00055344.PDF