Scope of vignette:
- authorised products (with marketing authorisation)
- decision process about routine use (and not individual requests for reimbursement)
- submissions for P&R made by manufacturers

Green = related to/any special considerations for rare disease and ultra-rare disease treatments

Canada	**Standard process (non-orphan drugs)** **Common Drug Review (CDR)**	**Standard process (non-orphan drugs)** **pan-Canadian Oncology Drug Review (pCODR)**	**Standard process (non-orphan drugs)** **INESSS (Quebec)**
Overview of health system	Tax based health insurance system. Federal government provides cash and tax transfers to the provinces and territories in support of health through the Canada Health Transfer. Regional provinces and territories administer and deliver health care services, (all plans are expected to meet national principles). Each provincial and territorial health insurance plan covers medically necessary hospital and doctors' services that are provided on a pre-paid basis, without direct charges at the point of service. The provincial and territorial governments fund these services with assistance from federal cash and tax transfers. [1]		
Overview of health system and P&R/HTA process	**National regulatory authority:** Health Canada approves drugs for use in Canada and issues MA. ***The processes for non-oncology and oncology drugs are almost identical, with the exception that drug committees and experts involved are different, and some timelines.** **Health Technology Assessment** CADTH is a country wide organization that provides recommendations to health care decision makers (federal, provincial, and territorial authorities) with the exception of Quebec (recommendations in Quebec are made by the HTA agency INESSS - only standard, no special OMP process). Reimbursement	**National regulatory authority:** Health Canada approves cancer drugs for use in Canada and issues MA. [2] ***The processes for non-oncology and oncology drugs are almost identical, with the exception that drug committees and experts involved are different, and some timelines.** **Health Technology Assessment** CADTH evaluates cancer drugs through the pan-Canadian Oncology Drug Review (pCODR) process and provides reimbursement recommendations to Federal drug plans, Provincial/Territorial (P/T) Ministries of Health (excluding Quebec) and Provincial Cancer Agencies. [3, 4]	**National regulatory authority:** Health Canada approves drugs for use in Canada and issues MA. The Institut national d'excellence en santé et en services sociaux (INESSS) evaluates drugs and sends recommendations to the minister of health for Quebec.

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	recommendations for drugs reviewed through the CDR process are provided by the CADTH Canadian Drug Expert Committee (CDEC) — an appointed, national, expert advisory committee. **Regional level:** CADTH's Drug Policy Advisory Committee (DPAC) provides strategic advice on drug policy issues and drug topics to CADTH. The DPAC Formulary Working Group provides advice and input on operational issues related to the CDR process. CDEC recommendations are non-binding to the public drug plans. Each drug plan makes its own reimbursement decisions based on the CDEC Final Recommendation and other factors. [2] **Some provinces have established processes for OMPs.	For pCODR, the expert drug committee is not the CDEC, but its equivalent: the CADTH pCODR Expert Review Committee (pERC - includes medical oncologists/hematologists, physicians, pharmacists, economists, an ethicist, and patient members). **Regional level:** CADTH's pCODR Advisory Committee (PAC) provides strategic advice on drug policy issues and oncology drug topics. The Provincial Advisory Group (PAG) provides advice and input on operational issues related to the pCODR process. pERC recommendations are non-binding to the public drug plans. Each drug plan makes its own reimbursement decisions based on the pERC Final Recommendation and other factors. [2]	
Differentiation of rare disease treatments in the P&R system	None		
Eligible medicines	New drugs, drugs with new indications, new combination products, biosimilar drugs, and subsequent-entry non-biologic complex drugs with a notice of compliance (NOC)(CADTH permits	New drugs, drugs with new indications, and biosimilars for the active treatment of a cancer (in selected circumstances, NOC not required).	

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	manufacturers to file submissions up to six weeks before anticipated issue date of NOC).		
Process	**Pre-submission Phase** • CADTH offers pre-submission meetings to help facilitate efficient preparation of applications (discussion between CADTH staff and manufacturer). • Applicants are required to provide a minimum of 30 business days advance notice before submitting their application. **Application and Screening Phase** • Submissions and resubmissions are screened against the requirements within 10 business days of receipt (5 business days for a biosimilar). • Once the file has been accepted, the review will be initiated within 10 business days and the manufacturer will be invoiced for the application fee. **Clinical and Economic Review** • CADTH conducts different types of reviews depending on the complexity of the drug under review (i.e., a standard or a tailored review). • For standard reviews, CADTH drafts clinical and pharmacoeconomic review reports in accordance with a review-specific protocol. The review provides an appraisal	**Pre-submission Phase** • CADTH offers pre-submission meetings to help facilitate efficient preparation of applications (discussion between CADTH staff and manufacturer). • Applicants are required to provide a minimum of 120 calendar days advance notice before submitting their application. **Application and Screening Phase** • Submissions and resubmissions are screened against the requirements within 10 business days of receipt. • Once the file has been accepted, the review will be initiated and the manufacturer will be invoiced for the application fee. **Clinical and Economic Review** • CADTH drafts a Clinical Guidance Report and an Economic Guidance Report in accordance with a review-specific protocol. The review provides an appraisal and interpretation of the best available evidence for the drug. Input from patient groups, clinical experts, and drug plans is considered in the review reports. • CADTH holds a checkpoint meeting with the applicant to clarify information in the submission and discuss issues related to the disclosure of information that is not in the	INESSS carries out drug evaluation mandate on the basis of five aspects (article 7 of its Act of Incorporation) • First, the Institute evaluates the therapeutic value of a drug. If it is not shown to satisfaction, a notice is sent to the Minister to. If it is Institute does considers that the therapeutic value is demonstrated, it sends its recommendation to the MoH after evaluating six key criteria, outlined below. • Following its assessment, INESSS makes a recommendation to the Minister of Health and Social Services concerning the RGAM List of Medications, the List of Medications - Establishments, or both. [1]

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	and interpretation of the best available evidence for the drug. Input from patient groups, clinical experts, and drug plans is considered in the review reports. • The draft review reports sent to the manufacturer for written comments. CADTH responds to the manufacturer's comments and revises the reports as required. The responses are sent to the manufacturer for information prior to the CDEC meeting. • The finalized review reports, comments and responses, and stakeholder input are sent to CDEC and the drug plans for review and consideration prior to the deliberations. **Recommendation** • The CDEC meeting is held and the committee deliberates on the clinical and economic evidence and stakeholder input. The committee votes on a recommendation for the drug under review and provides reasons for their decision. • CADTH issues an embargoed recommendation to the drug plans and the manufacturer. • Embargo period, followed by possible request for reconsideration by manufacturer, or request for clarification by drug plans, leading to further CDEC deliberation where the recommendation may be upheld or revised. • CADTH issues the CDEC final	public domain. • The finalized guidance reports and stakeholder input are sent to pERC and the drug plans for review and consideration prior to the deliberations. **Recommendation** • The pERC meeting is held and the committee deliberates on the clinical evidence, economic evidence, and stakeholder input. The committee votes on a recommendation for the drug under review and provides reasons for their decision. • CADTH posts an initial pERC recommendation and the Clinical and Economic Guidance Reports. • After the initial recommendation is posted, the submitter, manufacturer (if not the submitter), the registered patient advocacy group(s), and the PAG can provide feedback, which is submitted to pCODR using a feedback template • pERC Chair and three pERC members assess the feedback on the initial recommendation to determine if it is eligible to convert to a final recommendation without requiring pERC reconsideration . • For recommendations that are eligible for early conversion, the final recommendation is issued and posted on the CADTH website. • For recommendations that are not eligible for early conversion. The file is further discussed by	

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	recommendation to the manufacturer and drug plans. • Manufacturer completes redaction requests if applicable and the CDEC final recommendation is posted. CADTH review report(s) are subsequently posted. • Drug plans make listing decisions. [2]	pERC and the initial recommendation may be upheld or revised. • The final recommendation is issued and posted on the CADTH website. Feedback on the initial recommendation and the final Clinical and Economic Guidance reports and posted. • Drug plans make listing decisions.	
Disease specific expert input (e.g. clinicians or patients in any stage of the process)	**Stakeholder engagement** • **Patient input:** CADTH posts a call for patient input (using provided templates) via website, e-Alerts to subscribed patient groups, CADTH Twitter accounts 20 business days before the anticipated date of filing the application. Patient groups have a total of 35 business days to provide their input to CADTH. • **Clinician input:** All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. In the case of drugs that are undergoing or have undergone an expedited review by Health Canada for the indication of interest, multiple experts will be incorporated into the review team and supplemental clinical panels may be convened during	**Stakeholder engagement** • **Patient input:** CADTH posts a call for patient input (using provided templates) via website, e-Alerts to subscribed patient groups, CADTH Twitter accounts 20 business days before the anticipated date of filing the application. Patient groups have a total of 30 business days to provide their input to CADTH. • **Clinician input:** CADTH includes clinical experts in each pCODR review as members of a Clinical Guidance Panel who help ensure that the review of each cancer drug draws from the most important, relevant, and current clinical information. In addition, registered clinicians may submit information by completing a review-specific template. • **Drug plan input:** The participating drug plans provide input on each drug being reviewed through the pCODR process by identifying issues that may impact their ability to implement a pERC recommendation.	Experiential input is collected in various ways from health professionals, patients and caregivers, including, for example, through working groups and as part of the drug consultation process, literature reviews or questionnaires/interviews. [1]

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	the review to inform CDEC's recommendation. • **Drug plan input:** The participating drug plans provide input on each drug being reviewed through the CDR process by identifying issues that may impact their ability to implement a CDEC recommendation.		
Key domains in assessment	• Comparative clinical effectiveness • Cost-effectiveness • Other [3] [4]	• Comparative clinical effectiveness • Cost-effectiveness • Budget impact (provincial level) [2, 3]	• Clinical effectiveness • Cost-effectiveness • Budget impact [1]
Evidentiary requirements	Rarity of the condition for which the drug is indicated is a key consideration for determining when the committees could elect to issue a recommendation in favour of reimbursement despite uncertainty with the evidence available at the time of the deliberations.		RCTs are preferred, however, other types of studies may be accepted, but require justification. [1]
PROMs	In patient input phase, patient groups are asked open ended questions about their experiences --> HRQL is a standard endpoint that would be included in CADTH reviews.		Experiential input from patients, health professionals and caregivers contributes to process of assessing therapeutic value. --> Collected in various ways, including working groups and as part of drug consultation process, questionnaires, focus groups, interviews or literature search. [1]
Appraisal framework	CDEC considers the following information: • Input from patients and caregivers • Clinical evidence	pERC Deliberative Framework: • Clinical benefit • Alignment with patient values [3] • Safety • Efficacy • Effectiveness compared with	In addition to the key domains, INESSS evaluates its drugs based on the following additional key aspects:

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	• Economic evidence • Clinical expert opinion regarding place in therapy • Existing treatment options (e.g., what is or is not reimbursed and who is covered for reimbursement) • The submitted price of the drug under review and the publicly available prices of comparators • Applicant's requested reimbursement criteria (if any) and evidence supporting those criteria • Implementation considerations at the jurisdictional level • Unmet therapeutic need [3] [4]	alternatives • Therapeutic advantages and disadvantages relative to current accepted therapy • Implementation issues related to adoption feasibility • Unmet therapeutic need • Patient group input • Clinical expert opinion regarding place in therapy [2]	• Appropriateness of price • The consequences of the listing of the drug on the health of the population and on other components of the health and social services system • The desirability of listing the drug with regard to the purpose of the general prescription drug insurance plan • The identification and importance of the health need to be filled • The organizational capacity of the system to offer the drug Ethical and social issues [1]
Reimbursement decision	Based on provided evidence, CDEC or pERC members choose and justify one of three recommendation options: 1. Reimburse 2. Reimburse with conditions 3. Do not reimburse In exceptional cases where there is uncertain clinical and pharmacoeconomic evidence, the CADTH drug expert committees may issue a recommendation to reimburse with conditions, due to practical challenges in conducting robust clinical trials and pharmacoeconomic evaluations and in the presence of significant unmet medical need. In these situations, although there is uncertainty with the clinical evidence, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease. [3] [4]		Possible decisions: 1. List 2. List with conditions 3. Refusal to List INESSS may re-evaluate the registration of a drug, whether it is listed on the RGAM Medications List or on the List of Medications - Establishments. [1] In some exceptional files, a recommendation of promise of value was transmitted for decision, including a clinical monitoring (collection of data) for a re-assessment eventually.
Pricing process	• Consideration of the cost-effectiveness of the drug under review compared with appropriate comparators. • Consideration of the submitted price of the drug under review and		

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	the publicly available prices of comparators • Applicant's requested reimbursement criteria (if any) and evidence supporting those criteria CADTH committee's may include pricing conditions in their recommendations (e.g., reduction in price; cost not exceed available alternatives; must provide cost-savings relative to available alternatives)		
Managed entry agreements	OB to collect additional evidence for later reassessment (though not widely used by public drug plans currently).		Not permitted by law
Main challenges in appraising medicines for rare diseases (tick all that apply)	☒ Lack of good quality clinical data ☐ Lack of real world data ☐ Introducing value for money ☐ Monitoring treatment efficacy ☐ Managing budget impact ☐ Lack of criteria/transparency of OMP P&R processes ☒ Making arrangements to work for all stakeholders ☒ Lack of long-term meaningful outcomes ☒ Other, please specify : 1) Identifying clinical experts with expertise in the diagnosis and management of the condition, 2) Lack of robust economic evaluation, 3) Can be challenging to establish initiation, renewal, and discontinuation criteria with limited evidence, clinical experience, and poorly characterised natural history of disease.		
Impact of special processes	Changes to the recommendation in framework in 2016 (see detail under reimbursement decision) may have led to increase in the proportion of drugs for rare diseases that receive recommendations in favour of reimbursement by CADTH's expert review committees.		N/A
Proposed policy change	As with other jurisdictions, this continues to be an important topic for discussion in Canada. The review and reimbursement policies continue to evolve. In October 2018, a stakeholder consultation was held on the creation of supplemental process for complex/specialized drugs. It is anticipated that further details regarding this proposed process will be announced in 2019. A process to appraise rare disease treatments with evidence-based approaches is being developed. Possibilities of incorporating real world evidence and managed entry agreements are being investigated. It is expected that these changes will take place in 2020.		The minister of health for Quebec wants to have a national strategy for the care's trajectory, from screening to treatment… probably for mid-2020.

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	The Patented Medicine Prices Review Board is planning to update its guidelines by July 2020, to ensure prices of medicinal products are not excessive. These reforms are also intended to improve access to innovative medicines in terms of speed an better certainty. [9]		
Joint initiatives	National and international collaborations [5]: - CADTH is currently a key contributor to Health Canada's Regulatory Review of Drugs and Devices (R2D2) initiatives. Several of these projects may have implications for how drugs for rare diseases are evaluated and managed in Canada (e.g., Alignment of the Health Technology Assessor Review with the HPFB Review; Health System Need; Early Parallel Scientific Advice; and Real World Evidence). [6] - An Expensive Drug for Rare Diseases (EDRD) working group has been established in Canada which is led by Ontario, Alberta and British Columbia. CADTH is supporting this working group in their objective to develop a supplemental process for highly specialized/complex drugs and to receive stakeholder feedback on this proposal. - CADTH and INESSS are currently engaged in a pilot project to jointly engage with clinical experts on selected drug products. CADTH and INESSS will collaborate to establish the clinical panels, interact with the clinical experts on the panels, and summarize input and key information from the clinical panellists. Challenges in generating robust evidence due to the rarity of the condition is a key consideration when selecting drugs for this pilot project.		
SOURCES			
1	https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-system/canada.html	https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-system/canada.html	https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Processus/evolution_des_modalit%C3%A9s_Rx_juillet2018.pdf
2	https://www.cadth.ca/sites/default/files/cdr/process/Procedure_and_Guidelines_for_CADTH_CDR.pdf	https://www.cadth.ca/pcodr/about-pcodr	
3	https://www.cadth.ca/media/cdr/templates/pre-sub-phase/CDR_pCODR_recommendations_framework.pdf	https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-procedures.pdf	
4	https://www.cadth.ca/sites/default/files/pdf/es0326_drugs_for_rare_diseases.pdf	https://www.cadth.ca/media/cdr/templates/pre-sub-phase/CDR_pCODR_recommendati	

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		ons_framework.pdf	
5	https://www.cadth.ca/collaboration-and-outreach	https://www.cadth.ca/pcodr/process-in-brief	
6	https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html	https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-submission-guidelines.pdf	
7	https://cadth.ca/sites/default/files/corporate/CADTH-INESSS-Pilot_Announcement.pdf		
9	http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1466&lang=en		

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This vignette was compiled based on information provided by country experts and desk research. The information provided may be incomplete or contain inaccuracies. If you have any comments or updates, please email us at the following email addresses:

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