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Alignment of health technology assessments and price negotiations for new drugs for rare disorders in Canada: Does it lead to improved patient access?

Nigel S. B. Rawson[1,2,3]

[1]Eastlake Research Group, Oakville, ON, Canada

[2]Canadian Health Policy Institute, Toronto, ON, Canada

[3]Fraser Institute, Vancouver, BC, Canada

Corresponding author: EastlakeRG@gmail.com

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ABSTRACT

A previous assessment of submissions for rare disorder drugs made to the Canadian Agency for Drugs and Technologies in Health (CADTH) found that, from 2012, all positive recommendations included criteria advocating a price reduction. Since 2016, CADTH and the pan-Canadian Pharmaceutical Alliance (pCPA), which conducts drug price negotiations with manufacturers for all public drug programs, have aligned their processes. This analysis examined drugs for rare and ultra-rare disorders (DRDs and DURDs)—prevalence of ≤20 to >2 and ≤2 per 100,000, respectively—with a completed pCPA negotiation or no negotiation between 2014 and 2018, together with their reimbursement recommendations and listings in public drug programs. A positive recommendation led to a successful price negotiation for 81.8% and 78.6% of the DRD and DURD submissions and a negative recommendation to no negotiation for 100.0% and 66.7%. Less than half the recommendations for DURDs reported before 2016 mentioned the need for a substantial price reduction, but this increased to 80% in those reported from 2016 onwards. A successful price negotiation led to listing in the majority of the public drug programs and a negative recommendation usually led to no listing. The CADTH-pCPA alignment is working for the governments who own and fund public drug programs but has yet to lead to coverage for all appropriate patients in all provinces. There is still a way to go to ensure that patients with unmet needs can access high-cost innovative medicines that alleviate suffering, prevent premature death, and/or significantly improve their quality of life.

Keywords: *rare diseases, orphan drugs, health technology assessment, price negotiations, formulary listing, Canada*

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Health technology assessment of new prescription medicines is performed for all Canadian provincial and territorial public drug programs (except those in Quebec) by the Canadian Agency for Drugs and Technologies in Health (CADTH) through two processes: the pan-Canadian Oncology Drug Review (pCODR) for cancer drugs and the Common Drug Review (CDR) for all other drugs. At around 80%,[1] the pCODR positive reimbursement recommendation rate is significantly higher than the CDR rate of 50–55%.[2–4] Positive recommendations from both processes are commonly qualified with clinical criteria and/or a need for a price reduction. Negative recommendations are frequently based on the opinion that a drug's efficacy evidence is inadequate[2,5] despite having been assessed by Health Canada's regulatory review as acceptable. CADTH does not publicly acknowledge having a cost-effectiveness threshold for assessing drugs, but evidence exists to suggest that $50,000 per quality-adjusted life year is used, although not consistently applied.[2]

The pan-Canadian Pharmaceutical Alliance (pCPA) is the federal, provincial, and territorial governments' organization that negotiates prices of new and existing medicines with pharmaceutical manufacturers.[6] The pCPA's objectives include achieving consistent and lower drug costs for participating jurisdictions and improving consistency of coverage criteria among participating jurisdictions. The pCPA has been criticized for its lack of transparency,[7,8] but in May 2018 it published guidelines that describe the four phases of its method.[9] Following a health technology assessment recommendation, the pCPA considers whether a price negotiation will be opened with the manufacturer. For medicines for which a negotiation is begun, each government drug plan must declare whether it intends to join the negotiation. If an agreement is reached between the lead negotiating province and the manufacturer, both parties sign a letter of intent that implies the drug will be listed in any subsequent Product Licensing Agreement with an agreed price and listing criteria. Agreement terms are confidential.

Public drug plans are not mandated to list a medicine that has been successfully negotiated with the pCPA. Consequently, a listing agreement is not guaranteed in all participating plans. Using the basis of the terms in the letter of intent, manufacturers must negotiate individual Product Licensing Agreements with each participating jurisdiction. Information on how the public drug plans make funding decisions is not generally available.

A previous evaluation of submissions for rare disorder drugs made to the CDR between 2004 and February 3, 2016[5] found that, as the prevalence of the drug's indication decreased, the positive reimbursement recommendation rate also decreased, while an increase occurred in the proportion of recommendation reports in which attention was drawn to the drug's cost or the need for a price reduction. However, a change took place around 2012 in how high-cost rare disorder drugs are dealt with by the CDR. Before 2012, high cost was a factor in 85% of the negative reimbursement recommendations for rare disorder drugs, whereas between 2012 and February 2016, no rare disorder drug with a negative recommendation had its cost noted in the CDR report, but 100% of the rare disorder drugs with a positive recommendation included criteria advocating a price reduction or drawing attention to less expensive alternative therapies.

Since 2016, CADTH and the pCPA have aligned their processes. Ensuring a negative reimbursement recommendation results in no price negotiation and a positive recommendation sets up factors for inclusion in the price negotiation appears to be part of this alignment. Insufficient recommendations were available in the post-2015 period in the previous work to assess the impact

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of the CADTH-pCPA alignment on the outcomes of price negotiations and listing in public drug programs.

The objective of this analysis was to examine reimbursement recommendations for rare disorder drugs, results of the price negotiations, and listings in public drug programs for rare disorder drugs that had completed negotiations or for which the pCPA decided not to negotiate between 2014 and 2018. Since much effort has been put into aligning the processes, it is critical to assess whether the system is working.

METHODS

The monthly lists of active negotiations, completed negotiations with or without an agreement, and medications for which no negotiation has been undertaken published by the pCPA on its website between January 2014 and December 2018 were used to identify appropriate medicines. January 2014 was the starting point because pCPA outcomes are only available from this date.[10] If multiple negotiations had occurred for the same product and indication, the most recent outcome was recorded, but if a drug had more than one negotiation for different diagnoses, each one was included.

Only drugs for indications with a prevalence of ≤20 per 100,000 population were included in this evaluation. Prevalence figures were obtained from the Orphanet website[11] or up-to-date publications when Orphanet provided a wide range or no data. Health Canada has proposed a prevalence of <1 per 2,000 individuals to define a rare disorder,[12] but health conditions cover a wide spectrum from extremely common disorders through uncommon to rare and ultra-rare ones, and there is no consistent agreement on when a disorder is considered to be rare. For this evaluation, a prevalence of ≤20 per 100,000 was chosen to ensure that unquestionably rare or ultra-rare disorders were the focus. The drugs were divided into those for indications with a prevalence of ≤20 to >2 per 100,000 population—labeled drugs for rare disorders (DRDs)—and those for indications with a prevalence of ≤2 per 100,000 population—labeled drugs for ultra-rare disorders (DURDs).

Reimbursement recommendation reports for non-oncology drugs in the pCPA list were identified from the CDR's website.[13] Provincial formularies, special benefit lists and bulletins and the federal Non-Insured Health Benefits formulary available at the end of September 2019 were reviewed to assess how many drugs are listed in these public programs. Coverage criteria, where available, were evaluated for consistency between the CDR's recommendation and the public programs.

Since the positive rate of reimbursement recommendation for oncology drugs has been shown to be considerably higher than that for non-oncology drugs,[2–4] a similar evaluation of pCPA negotiations and pCODR recommendations[14] for oncology DURDs was performed for a comparison with the CDR recommendations. Information on listing in public drug plans (except for the Quebec and federal plans) was obtained from provincial funding summaries available from the pCODR website. Coverage in the Quebec and federal plans was obtained from the relevant websites.

RESULTS

Two of the drugs in the evaluation were for cystic fibrosis patients with specific gene mutations. Cystic fibrosis has an overall prevalence of ≤10 to >2 per 100,000. The combination product of lumacaftor and ivacaftor indicated for patients with homozygous F508del mutation, which constitutes about 50% of cystic fibrosis cases in Canada,[15] was considered to be a DRD. Ivacaftor, on the other hand, was included as a DURD because it is indicated for G551D, R117H, and other gating mutations, which have a prevalence of ≤2 per 100,000.[15]

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Fifteen pCPA price negotiations for non-oncology DRDs completed with or without success or for which none was begun between 2014 and 2018 were identified (Table 1). These concerned 14 drugs of which six (42.9%) were indicated for a genetic disorder. Nine price negotiations were successfully completed, and all these drugs had a positive CDR reimbursement recommendation. Two unsuccessful negotiations were for macitentan and riociguat, which had both received a positive reimbursement recommendation. Overall, nine (81.8%) of the 11 DRDs with a positive reimbursement recommendation had a successful price negotiation; all DRDs with a positive recommendation reported after 2015 were successfully negotiated. Each of the four DRDs for which the pCPA decided not to negotiate had a negative reimbursement recommendation. Four (57.1%) of the seven CDR recommendations reported after 2015 included a specific suggested price reduction to attain an incremental cost ratio of $50,000 or to bring the drug's price into line with a comparable drug. Based on the list prices provided in the CDR reports, the estimated daily cost of all but one DRD was under $500.

Seventeen pCPA negotiations concerned 13 DURDs of which 12 (92.3%) are indicated for genetic disorders (Table 2). Multiple price negotiations related to ivacaftor, which had three positive reimbursement recommendations, but only the pCPA negotiation for the G551D mutation was successfully completed (the pCPA decided not to negotiate for the other indications), and nitisinone for tyrosinemia type 1, for which three products from different companies were all successfully negotiated with the pCPA. For two drugs (asfotase alfa for hypophosphatasia and taliglucerase alfa for Gaucher's disease), the most recent price negotiation outcome was successful completion, but a previous negotiation for asfotase alfa had resulted in no agreement and the pCPA had originally decided not to negotiate for taliglucerase alfa. Reasons for the change in outcome are unknown. In addition, elosulfase alfa for mucopolysaccharidosis IVA originally received a negative recommendation from the CDR and the pCPA decided not to negotiate, but following a re-evaluation by the CDR, the drug received a positive recommendation and was successfully negotiated with the pCPA. One of the reasons for the change in recommendation was that mucopolysaccharidosis IVA is "a life-threatening, seriously debilitating disease that is chronic in nature, and no alternative enzyme treatments are available."[16]

Three (42.9%) of the seven reimbursement recommendations for DURDs reported before 2016 were negative and two of the three had no pCPA negotiation or an unsuccessful one. The CDR assessments for the four DURDs with positive recommendations reported before 2016 all mentioned the need for a price reduction, but none had a specific target. In contrast, all 10 reimbursement recommendations for DURDs reported after 2015 were positive, and eight (80.0%) CDR reports included the need for a substantial price reduction, with seven having a reduction of 60–97% specified. The DURDs were generally more costly than the DRDs; of those with a list price provided in the CDR report, almost 80% had an estimated daily cost of $500 or more.

Eight pCPA price negotiations for seven oncology DURDs completed with or without success or for which none was begun between 2014 and 2018 were identified (Table 3). Only two submissions (25.0%) received a negative recommendation for which there was no price negotiation. The other six submissions (75.0%) received a "fund conditional on cost-effectiveness improvement" recommendation (a statement commonly used by the pCODR) and had a successful price negotiation.

Tables 4–6 show the percentage of public drug programs listing the non-oncology DRDs and DURDs and the oncology DURDs by the end of September 2019, respectively. A successful price

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TABLE 1. Reimbursement Recommendation and Price Negotiation Outcome for Non-Oncology Drugs for Rare Disorders[a]

Generic name (brand name)	Clinical indication	Estimated daily cost[b]	Reimbursement recommendation			Price negotiation	
			Year	Outcome	Cost comment	Year	Most recent outcome
Riociguat (Adempas)	Pulmonary arterial hypertension, class IV	<$500	2014	LwC	Not cost-effective without substantial price reduction	2015	Completed
Stiripentol (Diacomit)	Dravet syndrome[c]	<$500	2014	LwC	Price reduction to improve cost-effectiveness	2015	Completed
Pasireotide (Signifor)	Cushing's disease	<$500	2015	DNR	–	2015	No negotiation
Everolimus (Afinitor)	Subependymal giant cell astrocytoma associated with tuberous sclerosis complex[c]	<$500	2015	DNR	Cost-effectiveness uncertain	2015	No negotiation
Macitentan (Opsumit)	Pulmonary arterial hypertension, classes II and III	<$500	2015	LwC	Price reduction required	2015	No agreement
Pirfenidone (Esbriet)	Idiopathic pulmonary fibrosis	<$500	2015	LwC	Substantial price reduction	2016	Completed
Nintedanib (Ofev)	Idiopathic pulmonary fibrosis	<$500	2015	LwC	Must not exceed cost of pirfenidone	2016	Completed
Riociguat (Adempas)	Pulmonary arterial hypertension, classes I, II & III	<$500	2015	LwC	More expensive than comparable drugs	2017	No agreement
Tolvaptan (Jinarc)	Autosomal dominant polycystic kidney disease	Redacted	2016	DNR	–	2016	No negotiation
Lumacaftor/ivacaftor (Orkambi)	Cystic fibrosis, homozygous F508del mutation[c]	$500–$999	2016	DNR	98% price reduction for incremental cost ratio of $50,000	2016	No negotiation
Sodium phenylbutyrate (Pheburane)	Urea cycle disorders[c]	<$500	2016	LwC	–	2017	Completed

TABLE 1. (Continued) Reimbursement Recommendation and Price Negotiation Outcome for Non-Oncology Drugs for Rare Disorders[a]

Selexipag (Uptravi)	Pulmonary arterial hypertension, classes II & III	<$500	2016	LwC	>42% price reduction for incremental cost ratio of $50,000	2017	Completed
Glycerol phenylbutyrate (Ravicti)	Urea cycle disorders[c]	<$500	2017	LwC	Price is 46% higher than comparable drug	2017	Completed
Obeticholic acid (Ocaliva)	Biliary cholangitis[c]	<$500	2017	LwC	>60% price reduction for incremental cost ratio of $50,000	2018	Completed
Tocilizumab (Actemra)	Giant cell arteritis	<$500	2018	LwC	Price reduction	2018	Completed

[a]Disorders with prevalence of ≤20 to >2 per 100,000; [b]From reimbursement recommendation report; [c]Genetic disorder.
DNR = do not reimburse, LwC = list with conditions.

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TABLE 2. Reimbursement Recommendation and Price Negotiation Outcome for Non-Oncology Drugs for Ultra-Rare Disorders[a]

Generic name (brand name)	Clinical indication	Estimated daily cost[b]	Reimbursement recommendation			Price negotiation	
			Year	Outcome	Cost comment	Year	Most recent outcome
Eculizumab (Soliris)	Atypical hemolytic uremic syndrome[c]	>$1,000	2013	DNR	Attention drawn to high cost	2016	No agreement
Ivacaftor (Kalydeco)	Cystic fibrosis G551D gating mutation[c]	$500–$999	2013	LwC	Not cost-effective without substantial price reduction	2014	Completed
Icatibant (Firazyr)	Hereditary angioedema[c]	Redacted	2014	LwC	Price reduction	2015	Completed
Ivacaftor (Kalydeco)	Cystic fibrosis gating mutations[c]	$500–$999	2014	LwC	Substantial price reduction	2017	No negotiation
Lomitapide (Juxtapid)	Homozygous familial hypercholesterolemia[c]	>$1,000	2015	DNR	Attention drawn to high cost	2015	No negotiation
Taliglucerase alfa (Elelyso)	Gaucher's disease[‡]	$500–$999	2015	DNR	Cost-effectiveness not assessable	2018	Completed
Ivacaftor (Kalydeco)	Cystic fibrosis R117H gating mutation[c]	$500–$999	2015	LwC	Substantial price reduction to improve cost-effectiveness	2017	No negotiation
Asfotase alfa (Strensiq)	Hypophosphatasia[c]	>$1,000	2016	LwC	Substantial price reduction	2018	Completed
Elosulfase alfa (Vimizim)	Mucopolysaccharidosis IVA[c]	Redacted	2016	LwC	97% price reduction for incremental cost ratio of $100,000	2018	Completed
Teduglutide (Revestive)	Short bowel syndrome	Redacted	2016	LwC	80% price reduction for incremental cost ratio of $100,000	2018	Completed
Eliglustat (Cerdelga)	Gaucher's disease[c]	>$1,000	2017	LwC	Not to exceed similar drugs	2018	No agreement
Nusinersen (Spinraza)	Spinal muscular atrophy[c]	>$1,000	2017	LwC	95% price reduction for incremental cost ratio of >$400,000	2018	Completed
Migalastat (Galafold)	Fabry disease[c]	$500–$999	2018	LwC	Not to exceed comparable drugs	2018	Completed
Cysteamine (Procysbi)	Nephropathic cystinosis[c]	$500–$999	2018	LwC	95% price reduction for incremental cost ratio of >$100,000	2018	Completed
Nitisinone (Orfadin)	Tyrosinemia type 1[c]	<$500	2018	LwC	>74% price reduction for incremental cost ratio of <$100,000	2018	Completed
Nitisinone (MDK-Nitisinone)	Tyrosinemia type 1[c]	<$500	2018	LwC	60% price reduction	2018	Completed
Nitisinone (Nitisinone)	Tyrosinemia type 1[c]	<$500	2018	LwC	74% price reduction	2018	Completed

[a]Disorders with prevalence of ≤2 per 100,000; [b]From reimbursement recommendation report; [c]Genetic disorder. DNR = do not reimburse; LwC = list with conditions.

TABLE 3. Reimbursement Recommendation and Price Negotiation Outcome for Oncology Drugs for Ultra-Rare Disorders[a]

Generic name (brand name)	Clinical indication	Estimated daily cost[b]	Reimbursement recommendation		Price negotiation	
			Year	Outcome	Year	Most recent outcome
Regorafenib (Stivarga)	Gastrointestinal stromal tumor	Redacted	2014	Fund conditional on cost-effectiveness improvement	2017	Completed
Romidepsin (Istodax)	Peripheral t-cell lymphoma	$500–$999	2015	Fund conditional on cost-effectiveness improvement	2015	Completed
Bosutinib (Bosulif)	Chronic myeloid leukemia	<$500	2015	Fund conditional on cost-effectiveness improvement	2015	Completed
Siltuximab (Sylvant)	Castleman's disease	<$500	2015	Fund conditional on cost-effectiveness improvement	2016	Completed
Ibrutinib (Imbruvica)	Waldenstrom's macroglobulinemia	<$500	2016	Do not reimburse[c]	2016	No negotiation
Trabectedin (Yondelis)	Liposarcoma or leiomyosarcoma	<$500	2016	Do not reimburse[c]	2016	No negotiation
Ibrutinib (Imbruvica)	Mantle cell lymphoma	<$500	2016	Fund conditional on cost-effectiveness improvement[d]	2017	Completed
Vandetanib (Caprelsa)	Medullary thyroid cancer	<$500	2017	Fund conditional on cost-effectiveness improvement[d]	2018	Completed

[a]Oncology disorders with prevalence of ≤2 per 100,000; [b]From reimbursement recommendation report; [c]Not cost-effective and attention drawn to high cost; [d]Attention drawn to high cost.

TABLE 4. Public Drug Plan Listings for Non-Oncology Drugs for Rare Disorders[a]

Generic name (brand name)	Clinical indication	Price negotiation		Drug plan listings[b]	
		Year	Most recent outcome	No.	%
Riociguat (Adempas)	Pulmonary arterial hypertension, class IV	2015	Completed	8	72.7
Stiripentol (Diacomit)	Dravet syndrome[c]	2015	Completed	10	90.9
Pirfenidone (Esbriet)	Idiopathic pulmonary fibrosis	2016	Completed	11	100.0
Nintedanib (Ofev)	Idiopathic pulmonary fibrosis	2016	Completed	11	100.0
Sodium phenylbutyrate (Pheburane)	Urea cycle disorders[c]	2017	Completed	8	72.7
Selexipag (Uptravi)	Pulmonary arterial hypertension, classes II and III	2017	Completed	10	90.9
Glycerol phenylbutyrate (Ravicti)	Urea cycle disorders[c]	2017	Completed	9	81.8
Obeticholic acid (Ocaliva)	Biliary cholangitis[c]	2018	Completed	10	90.9
Tocilizumab (Actemra)	Giant cell arteritis	2018	Completed	9	81.8
Macitentan (Opsumit)	Pulmonary arterial hypertension, classes II and III	2015	No agreement	1	9.1
Riociguat (Adempas)	Pulmonary arterial hypertension, classes I, II, and III	2017	No agreement	9	81.8
Pasireotide (Signifor)	Cushing's disease	2015	No negotiation	0	0.0
Everolimus (Afinitor)	Subependymal giant cell astrocytoma associated with tuberous sclerosis complex[c]	2015	No negotiation	1	9.1
Tolvaptan (Jinarc)	Autosomal dominant polycystic kidney disease	2016	No negotiation	0	0.0
Lumacaftor/ivacaftor (Orkambi)	Cystic fibrosis, homozygous F508del mutation[c]	2016	No negotiation	0	0.0

[a]Disorders with prevalence of ≤20 to >2 per 100,000; [b]As of September 30, 2019; [c]Genetic disorder.

negotiation led to listing in six or more of the public drug programs of 100% of the non-oncology DRDs and 83.3% of the oncology DURDs but only 33.3% of the non-oncology DURDs. A negative recommendation usually led to no negotiation and no listing. The non-oncology DURDs with a successful price negotiation listed by less than half the public drug programs (asfotase alfa for hypophosphatasia, elosulfase alfa for mucopolysaccharidosis IVA, migalastat for Fabry disease, nitisinone for tyrosinemia type 1, taliglucerase alfa for Gaucher's disease, and teduglutide for short bowel syndrome) all had pCPA negotiations completed in 2018.

Table 7, which shows numbers of listings of the DRDs, DURDs, and oncology DURDs in each of the provincial and federal plans as of September 30, 2019, demonstrates that more than three-quarters of the DRDs with a completed pCPA negotiation were listed in nine plans (the exceptions were Prince Edward Island and the Non-Insured Health Benefits plan), and more

TABLE 5. Public Drug Plan Listings for Non-Oncology Drugs for Ultra-Rare Disorders[a]

Generic name (brand name)	Clinical indication	Price negotiation		Drug plan listings[b]	
		Year	Most recent outcome	No.	%
Ivacaftor (Kalydeco)	Cystic fibrosis G551D gating mutation[c]	2014	Completed	8	72.7
Icatibant (Firazyr)	Hereditary angioedema[c]	2015	Completed	10	90.9
Taliglucerase alfa (Elelyso)	Gaucher's disease[c]	2018	Completed	4	36.4
Asfotase alfa (Strensiq)	Hypophosphatasia[c]	2018	Completed	2	18.2
Elosulfase alfa (Vimizim)	Mucopolysaccharidosis IVA[c]	2018	Completed	1	9.1
Teduglutide (Revestive)	Short bowel syndrome	2018	Completed	5	45.5
Nusinersen (Spinraza)	Spinal muscular atrophy[c]	2018	Completed	7	63.6
Migalastat (Galafold)	Fabry disease[c]	2018	Completed	4	36.4
Cysteamine (Procysbi)	Nephropathic cystinosis[c]	2018	Completed	7	63.6
Nitisinone (Orfadin)	Tyrosinemia type 1[c]	2018	Completed	5	45.5
Nitisinone (MDK-Nitisinone)	Tyrosinemia type 1[c]	2018	Completed	4	36.4
Nitisinone (Nitisinone)	Tyrosinemia type 1[c]	2018	Completed	4	36.4
Eculizumab (Soliris)	Atypical hemolytic uremic syndrome[c]	2016	No agreement	1	9.1
Eliglustat (Cerdelga)	Gaucher's disease[c]	2018	No agreement	0	0.0
Lomitapide (Juxtapid)	Homozygous familial hypercholesterolemia[c]	2015	No negotiation	1	9.1
Ivacaftor (Kalydeco)	Cystic fibrosis R117H gating mutation[c]	2017	No negotiation	0	0.0
Ivacaftor (Kalydeco)	Cystic fibrosis gating mutations[c]	2017	No negotiation	0	0.0

[a]Disorders with prevalence of ≤2 per 100,000; [b]As of September 30, 2019; [c]Genetic disorder.

TABLE 6. Public Drug Plan Listings for Oncology Drugs for Ultra-Rare Disorders[a]

Generic name (brand name)	Clinical indication	Price negotiation		Drug plan listings[b]	
		Year	No.	No.	%
Regorafenib (Stivarga)	Gastrointestinal stromal tumor	2017	Completed	10	90.9
Romidepsin (Istodax)	Peripheral t-cell lymphoma	2015	Completed	9	81.8
Bosutinib (Bosulif)	Chronic myeloid leukemia	2015	Completed	9	81.8
Siltuximab (Sylvant)	Castleman's disease	2016	Completed	5	45.5
Ibrutinib (Imbruvica)	Mantle cell lymphoma	2017	Completed	10	90.9
Vandetanib (Caprelsa)	Medullary thyroid cancer	2018	Completed	6	54.5
Ibrutinib (Imbruvica)	Waldenstrom's macroglobulinemia	2016	No negotiation	0	0.0
Trabectedin (Yondelis)	Liposarcoma or leiomyosarcoma	2016	No negotiation	0	0.0

[a]Oncology disorders with prevalence of ≤2 per 100,000; [b]As of September 30, 2019.

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TABLE 7. Numbers of Listings for Drugs for Rare Disorders, Ultra-Rare Disorders, and Ultra-Rare Oncology Disorders, by Public Drug Plan[a]

Drug plan	Drugs for rare disorders[b]			Drugs for ultra-rare disorders[c]			Drugs for ultra-rare oncology disorders[d]	
	Negotiation completed (n = 9)	No agreement (n = 2)	No negotiation (n = 4)	Negotiation completed (n = 12)	No agreement (n = 2)	No negotiation (n = 3)	Negotiation completed (n = 6)	No negotiation (n = 2)
Alberta	7 (77.8%)	0 (0.0%)	0 (0.0%)	11 (91.7%)	0 (0.0%)	0 (0.0%)	5 (83.3%)	0 (0.0%)
British Columbia	8 (88.9%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	5 (83.3%)	0 (0.0%)
Manitoba	9 (100.0%)	1 (50.0%)	0 (0.0%)	9 (75.0%)	0 (0.0%)	0 (0.0%)	6 (100.0%)	0 (0.0%)
New Brunswick	9 (100.0%)	1 (50.0%)	0 (0.0%)	8 (66.7%)	0 (0.0%)	0 (0.0%)	6 (100.0%)	0 (0.0%)
Newfoundland and Labrador	8 (88.9%)	1 (50.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	3 (50.0%)	0 (0.0%)
Nova Scotia	9 (100.0%)	1 (50.0%)	0 (0.0%)	9 (75.0%)	0 (0.0%)	0 (0.0%)	4 (66.7%)	0 (0.0%)
Ontario	9 (100.0%)	1 (50.0%)	1 (25.0%)	7 (58.3%)	1 (50.0%)	1 (33.3%)	6 (100.0%)	0 (0.0%)
Prince Edward Island	5 (55.6%)	1 (50.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)
Quebec	7 (77.8%)	2 (100.0%)	0 (0.0%)	8 (66.7%)	1 (50.0%)	1 (33.3%)	3 (50.0%)	0 (0.0%)
Saskatchewan	9 (100.0%)	1 (50.0%)	0 (0.0%)	4 (33.3%)	0 (0.0%)	0 (0.0%)	6 (100.0%)	0 (0.0%)
Non-Insured Health Benefits	6 (66.7%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (66.7%)	0 (0.0%)

[a]As of September 30, 2019; [b]Disorders with prevalence of ≤20 to >2 per 100,000; [c]Disorders with prevalence of ≤2 per 100,000; [d]Oncology disorders with prevalence of ≤2 per 100,000.

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than two-thirds of the oncology DURDs with a completed negotiation were listed in eight plans (the exceptions were Newfoundland and Labrador, Prince Edward Island and Quebec). In addition, nine of the plans listed at least one of the two DRDs for which there was no price agreement. However, only five plans listed two-thirds or more of the non-oncology DURDs with a completed negotiation, with British Columbia, Newfoundland and Labrador, Prince Edward Island, Saskatchewan, and the Non-Insured Health Benefits plan listing none to a third.

Coverage in a public drug program is almost always conditional upon clinical criteria being satisfied; only pirfenidone and nintedanib for idiopathic pulmonary fibrosis and glycerol phenylbutyrate for urea cycle disorders were accessible in Quebec without conditions. The criteria generally required patients to have been diagnosed with the disorder, under the care of a physician experienced with treating the disorder, and perhaps an age limitation, failed control on current therapy, or a dietary restriction. Other criteria were more extensive, for example, the initiation criteria for spinal muscular atrophy.[17] However, the public drug program access criteria were usually consistent with the CADTH recommended criteria.

DISCUSSION

This evaluation has some limitations. A relatively small number of drugs were included. The analysis is based on the publicly available information in the formularies and benefit lists of the public drug programs, which do not always include all covered medications. Although the prevalence of the indications of the drugs was obtained from reliable sources, estimating the prevalence for rare disorders accurately can be difficult. Nevertheless, the categorization used was designed to ensure that the assessment focused on indisputably rare disorders.

The evaluation demonstrated similarities between positive reimbursement recommendation rates for the non-oncology DRDs and DURDs, and both showed an increase in the positive recommendation rate after 2015. In post-2015 recommendations for both DRDs and DURDs, there was an increase in the number of reports with a specified percentage reduction in the drug's list price to achieve an incremental cost ratio of $50,000 for DRDs and $100,000 (or in some cases, a higher value) for DURDs. These percentages were frequently large, particularly for DURDs where they were 60% or higher. Nevertheless, a successful price negotiation was completed for 45.5% of the DRDs and 78.6% of the DURDs with a positive CDR recommendation report specifying the need for a substantial price reduction. Since pCPA negotiations are confidential, any bargained reduction in price is only known to the manufacturer and governments, but it is reasonable to assume that the agreement required a concession from the company. However, it seems unlikely that price reductions exceeded 60%.

Positive recommendations issued by pCODR almost always state that the drug should be funded conditional on cost-effectiveness improvement but do not specify the level of price reduction desired. Price negotiations for all the oncology DURDs with a positive reimbursement recommendation were successful and, unlike the non-oncology DURDs, were listed in most provincial formularies. Oncology drugs tend to have a higher priority in Canada, with a higher proportion receiving an expedited regulatory review[18] and a higher positive reimbursement recommendation rate.[2–4]

The evaluation indicates that the alignment between CADTH and the pCPA is working for the federal, provincial, and territorial governments who own, fund, and manage not only the public drug programs but also CADTH and the pCPA,[10,19] because drugs that receive a negative reimbursement recommendation usually do not undergo a price negotiation and those that receive a positive recommendation generally have a

successful negotiation. However, since the public drug programs participating in a successful pCPA negotiation are not mandated to cover the medication, something of a "no means no and yes means maybe"[20] approach appears to remain for non-oncology DURDs. A successful price negotiation is not conditional upon a positive health technology assessment recommendation nor does it guarantee that the drug will be listed in most plans.

Moreover, drugs may only be covered if a patient satisfies clinical criteria that apply to few individuals and are excessive. Thus, the listing of a drug in a public program does not necessarily result in every patient with the disorder being able to access it. For example, eculizumab for atypical hemolytic uremic syndrome (aHUS) is listed in Ontario but only some patients have been able to obtain coverage, while the age limit on access to nusinersen prevents adults with spinal muscular atrophy from receiving benefits the drug may provide.[21] Access for some drugs may be approved on a case-by-case basis, but without information regarding the selection criteria, it is unknown whether access is appropriate or fair or whether it is arbitrary or discriminatory.

Health Canada's regulatory review is designed to ensure that only drugs with demonstrated efficacy, safety, and manufacturing quality are approved for use by Canadians. Once a drug has passed this review, Canadians want to be able to access its potential benefits without needing to be a billionaire. They are especially concerned when CADTH duplicates part of Health Canada's regulatory role and comes to a negative conclusion regarding a drug's efficacy, which is commonly one of the reasons for a negative reimbursement recommendation.[22] CADTH's approach to health technology assessment tends to be a narrow one requiring evidence from randomized clinical trials, which are often difficult to accomplish for rare disorders. The assessment report of eculizumab for aHUS, which has an incidence of one to two per million individuals,[23] noted that no randomized controlled trials were identified so that the CDR's assessment was based on three uncontrolled studies, which led to a negative recommendation because "the clinical benefit of eculizumab could not be adequately established."[24] Numerous case reports demonstrating the benefits of eculizumab and expert opinions that the drug represents a breakthrough in treating aHUS seem to have played no role in the CDR evaluation. In contrast, England's National Institute for Health and Care Excellence recommended funding for eculizumab for aHUS under its highly specialized technologies program, which has a much higher cost-effectiveness threshold, because studies of the drug produced cost-effective benefit "gains of a magnitude that is rarely seen for any new drug treatment."[25] Pasireotide for Cushing's disease, everolimus for subependymal giant cell astrocytoma associated with tuberous sclerosis complex, tolvaptan for autosomal dominant polycystic kidney disease, lomitapide for homozygous familial hypercholesterolemia, taliglucerase alfa for Gaucher's disease, ibrutinib for Waldenstrom's macroglobulinemia, and trabectedin for liposarcoma were also recommended for funding by the National Institute for Health and Care Excellence but not by CADTH or Quebec's agency. A specialized approach to health technology assessment with a higher value threshold for DRDs and particularly for DURDs is needed in Canada.

Recent changes introduced or planned by the federal government will radically alter the Canadian pharmaceutical environment, especially in relation to access to drugs for patients with unmet needs for new therapies. As part of its present focus on "affordability, accessibility and appropriate use of prescription drugs,"[26] the current government has made major revisions in the price review regulations of the agency that sets ceiling prices for patented medicines sold in Canada. The new regulations and guidelines replace countries that have relatively higher drug

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prices with lower price countries in the agency's international price comparison analysis, enforce a hard and low cost-effectiveness threshold using CADTH assessments as the benchmark, impose a reduction in a drug's price if its annual sales in Canada exceed a defined level, and require pharmaceutical companies to divulge information to the agency on confidential rebates and other commercial terms negotiated with payers in Canada.[27] These changes will force manufacturers of high-cost drugs to reduce their list prices by 45–75%,[28] perhaps more, which is an unsustainable business model.

These changes will endanger the launch of all new medicines in Canada because the country's attractiveness as a jurisdiction in which pharmaceutical companies want to perform clinical trials or seek regulatory approval for new products will be significantly reduced.[29–31] Manufacturers of new specialty high-cost medications, many of which are for rare disorders, will be particularly impacted and may decide that the Canadian market is not worth the risk of failing to secure a reasonable price, especially if confidential rebates and other commercial terms negotiated with Canadian drug insurance programs become known in other jurisdictions. If this occurs, it will eliminate access for all patients, including those with private insurance. Even if manufacturers decide to bring their medicines to Canada, they may only do so after launching them in other countries first, which will not deny access to Canadians but will certainly lead to considerable delays with additional suffering beyond that already endured.

Another significant change on the horizon is the federal government's intention to introduce a national pharmacare program,[32] which could further delay or deny access to new innovative drugs if it is limited in scope,[33] as the resources promised in the government's recent election platform suggest will be the case.[34] The present focus of the government in this initiative appears to be on ensuring that Canadians who do not have drug coverage or those that do have coverage but cannot afford the required copayments and deductibles are able to access commonly prescribed, primary care medicines. Although this is an important goal, national pharmacare should do more. The government has also laid out its intention to implement a national strategy for access to medicines for rare disorders, which includes funding of $500 million per year starting in 2022–2023, but the expense of these drugs is over-emphasized, moving the issue from providing access to medicines that can deliver significant benefits to one of affordability. High-cost breakthrough drugs that fulfill unmet needs for patients and also reduce expensive hospitalizations and other health services but are unaffordable for the average Canadian must also be part of national pharmacare, especially if the desire for equity across Canada is to be realized.[35]

CONCLUSION

The CADTH-pCPA alignment is working for the governments who own CADTH, the pCPA, and the public drug programs, but it has yet to lead to improved access in a timely manner for all appropriate patients in all provinces. There is still a way to go to ensure that patients with unmet needs can access high-cost innovative medicines that alleviate suffering, prevent premature death and/or significantly improve their quality of life. CADTH staff have suggested that it may be inappropriate for CADTH to apply its standard appraisal approach to DURDs,[36] but a more urgent need exists for the federal, provincial, and territorial governments to implement a long-overdue, comprehensive rare disease strategy[37] that would include ensuring that medications for these disorders are reviewed and reimbursed quickly and equitably to provide adequate health care to all Canadians that need these treatments. The federal government's revisions to the pharmaceutical environment in Canada are more likely to reduce access to costly breakthrough medicines, rather than enhance it.

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CONFLICTS OF INTEREST

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Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by the author.

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