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Regulatory approval and public drug plan listing of new drugs for rare disorders in Canada and New Zealand

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ABSTRACT

A previous assessment of the alignment of health technology assessments and price negotiations for new drugs for rare disorders in Canada completed between 2014 and 2018 demonstrated that it is working for governments but has yet to lead to improved access in a timely manner for all appropriate patients in all provinces. In this analysis, drugs for rare and ultra-rare disorders with a completed price negotiation or no negotiation between 2014 and 2018 in Canada, and their reimbursement recommendations and listings in Canadian public drug programs are compared with their regulatory approval in New Zealand and listing in the New Zealand National Formulary. The results show that pharmaceutical manufacturers generally seek regulatory approval for rare disorder drugs in Canada before New Zealand, and fewer rare disorder medicines receive regulatory approval in New Zealand. One reason for this difference might be New Zealand's smaller population. However, another reason is likely the restrictive drug formulary in New Zealand. Drugs not given coverage in New Zealand are frequently made unavailable by the manufacturer. Planned changes to Canada's pricing regulations and guidelines will significantly diminish the country's attractiveness as a place in which pharmaceutical companies want to do business, which has the potential to negatively impact the health of all Canadians irrespective of whether they have private or public drug coverage.

Keywords: *Canada, drugs, formulary listing, New Zealand, rare disorders, regulatory approval*

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INTRODUCTION

The Canadian federal government is heavily focused on "affordability, accessibility, and appropriate use of prescription drugs".[1] One aspect of this policy is the far-reaching revisions being made to the regulations and guidelines of the Patented Medicine Prices Review Board (PMPRB), which is the government agency that, for the past 30 years, has set ceiling prices for new medicines sold in Canada.[2] The changes,[3] which take effect in July 2020, include replacing higher drug price countries in the PMPRB's international price comparison analysis with lower price countries, assessing the "value" of each new drug against a threshold of $60,000 per quality-adjusted life-year for all drugs, and requiring pharmaceutical manufacturers to divulge information on confidential price rebates negotiated in Canada. The government anticipates that the changes will drive down prices by 40% on average.[4] "On average" implies that some price reductions will be much greater. Canada's health technology assessment agencies do not set prices, but one frequently indicates in its reimbursement recommendation reports that substantial reductions of 40–98%[5] are required to achieve cost-effectiveness at a lower threshold.

Canada already has many barriers that pharmaceutical manufacturers must overcome to bring a new medicine to patients,[6] which place it among countries with the lowest reimbursement coverage rates and the slowest coverage approval times.[7,8] In recent years, almost 80% of new therapeutic drugs approved in Canada, the United States, and Europe were submitted for review by Health Canada later than to the Food and Drug Administration and the European Medicines Agency, with a median delay of a year between approval by the first agency and approval in Canada.[9] The changes in the PMPRB's role will reduce the attractiveness of Canada as a country in which to invest in research and development[10] and to seek regulatory and reimbursement approval for new medicines,[11] If severe price reductions are mandated in Canada,[12] they will be a disincentive to bringing new drugs to Canada, which will delay or deny patients access to new innovative medications and make access to them much more limited.

The federal government intends the changes to the PMPRB to be a step toward a national pharmacare program. Some Canadian academics,[13,14] endorsed by many others, have encouraged the government to introduce a strong cost-containment approach of the type used by the Pharmaceutical Management Agency (PHARMAC) in New Zealand. PHARMAC is a government agency whose role within the government-funded health system is "to make decisions on which medicines and medical devices are funded in order to get the best health outcomes from within the available funding".[15]

The objective of this analysis was to compare listings in Canadian provincial and federal public drug plans for new drugs for rare disorders with completed or refused price negotiations between January 2014 and December 2018 assessed in a previous analysis[5] with coverage for the same drugs in the New Zealand National Formulary (the Pharmaceutical Schedule) by December 2019.

METHODS

Non-oncology drugs for disorders with a prevalence of ≤20 per 100,000 population and a price negotiation completed with or without agreement or where a decision was made not to negotiate between January 2014 and December 2018 were included in this analysis. January 2014 was the starting point because negotiation outcomes are only available from this date.[16] 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]). Drugs for oncology disorders with a prevalence of ≤2 per 100,000 population (ODURDs) and a price negotiation completed with or without agreement or where a decision was made not to negotiate between January 2014 and December 2018 were also included.

Reimbursement recommendation reports for the DRDs, DURDs, and ODURDs were identified from the websites of the Canadian Agency for Drugs and Technologies in Health.[17,18] The most up-to-date provincial formularies, special benefit lists, and bulletins available at the end of December 2019 were reviewed to identify the DRDs and DURDs listed in these public drug programs. Information on the ODURDs listed in public drug plans (except for the Quebec and federal National Insured Health Benefits plans) was obtained from provincial funding summaries available from Canadian Agency for Drugs and Technologies in Health's website. Coverage in the Quebec and federal plans was obtained from their websites.

Information on new drug applications approved in New Zealand was obtained from the website of the Medicines and Medical Devices Safety Authority, known as Medsafe,[19] for the drugs approved in Canada. Medsafe data also provide information regarding drugs that are unavailable. A product deemed unavailable in New Zealand is "where a product has been granted consent, but the company has advised in writing that they do not supply the product upon request or actively market it".[20] The Medsafe website allows users to identify applications submitted from 2006 onward that were refused by the authority. This facility was used to assess whether any of the new DRDs, DURDs, and ODURDs approved in Canada had been submitted in New Zealand and subsequently denied approval. Drugs listed in the Pharmaceutical Schedule,[21] were identified.

RESULTS

For 14 DRDs, 14 DURDs, and eight ODURDs given regulatory approval in Canada between 2014 and 2018 (Tables 1 to 3), the corresponding numbers approved in New Zealand to the end of 2019 were 10 (71.4%), seven (50.0%), and four (50.0%). Of the 21 drugs approved in New Zealand, 16 (76.2%) were given approval in the year after being approved in Canada or later. One DRD (stiripentol) was approved via a special program in New Zealand (Table 1). None of the drugs approved in Canada were denied approval in New Zealand.

Ten of the 14 DRDs, 11 of the 14 DURDs, and six of the eight ODURDs approved in Canada received a positive reimbursement recommendation from the Canadian Agency for Drugs and Technologies in Health, and a successful price negotiation was completed for almost all these medications. Nine DRDs (90.0%) and all six ODURDs (100.0%) with a positive reimbursement recommendation and a successful price negotiation were listed in six or more Canadian public drug plans by the end of 2019 compared with four DURDs (36.4%).

Only one DURD and one ODURD with a negative reimbursement recommendation had a successful price negotiation. Few of these drugs were listed by Canadian public drug plans.

Five DRDs, two DURDs, and one ODURD (50.0, 28.6, and 25.0%, respectively) were listed in the New Zealand Pharmaceutical Schedule at the end of 2019. Four DRDs (40.0%) and four DURDs (57.1%) with regulatory approval in New Zealand were reported as being unavailable.

DISCUSSION

These results demonstrate that pharmaceutical manufacturers generally seek regulatory approval for rare disorder drugs in Canada before doing so in New Zealand, just as they do for all medicines,[22] and fewer rare disorder medicines receive

TABLE 1. Approval and Reimbursement Status of Drugs for Rare Disorders[a] in Canada and New Zealand

		Canada				New Zealand		
Generic name (brand name)	**Clinical indication**	**Regulatory approval**	**Reimbursement recommendation**	**Price negotiation**	**Plans listing drug[b]**	**Regulatory approval**	**Available**	**Formulary listing**
Macitentan (Opsumit)	Pulmonary arterial hypertension	2013	Positive	No agreement	1 (9.1%)	2014	No[c]	No
Riociguat (Adempas)	Pulmonary arterial hypertension	2013	Positive	Completed	9 (81.8%)	2014	No[c]	No
Selexipag (Uptravi)	Pulmonary arterial hypertension	2016	Positive	Completed	10 (90.9%)	2016	No[c]	No
Pirfenidone (Esbriet)	Idiopathic pulmonary fibrosis	2012	Positive	Completed	11 (100.0%)	2016	Yes	Yes
Nintedanib (Ofev)	Idiopathic pulmonary fibrosis	2015	Positive	Completed	11 (100.0%)	2016	Yes	Yes
Sodium phenylbutyrate (Pheburane)	Urea cycle disorders	2015	Positive	Completed	8 (72.7%)	2015	Yes	Yes
Glycerol phenylbutyrate (Ravicti)	Urea cycle disorders	2016	Positive	Completed	9 (81.8%)	-	No	No
Stiripentol (Diacomit)	Dravet syndrome	2012	Positive	Completed	10 (90.9%)	-	Yes[d]	Yes
Obeticholic acid (Ocaliva)	Biliary cholangitis	2017	Positive	Completed	10 (90.9%)	-	No	No
Tocilizumab (Actemra)	Giant cell arteritis	2017	Positive	Completed	9 (81.8%)	2015	Yes	No
Everolimus (Afinitor)	Subependymal giant cell astrocytoma associated with tuberous sclerosis complex	2011	Negative	None	2 (18.2%)	2012	Yes	Yes
Pasireotide (Signifor)	Cushing's disease	2013	Negative	None	0 (0.0%)	2015	No[c]	No
Lumacaftor/ivacaftor (Orkambi)	Cystic fibrosis, homozygous F508del mutation	2016	Negative	None	0 (0.0%)	-	No	No
Tolvaptan (Jinarc)	Autosomal-dominant polycystic kidney disease	2015	Negative	None	0 (0.0%)	2019	Yes	No

[a] *Drugs for disorders with prevalence of ≤20 and >2 per 100,000 with a price negotiation outcome in Canada reported between January 2014 and December 2018.*

[b] *As of December 31, 2019.*

[c] *Has regulatory approval but is unavailable from manufacturer in New Zealand.*

[d] *Available under Named Patient Pharmaceutical Assessment framework (https://www.pharmac.govt.nz/tools-resources/forms/exceptional-circumstances/nppa-decisions/)*

TABLE 2. Approval and Reimbursement Status of Drugs for Ultra-Rare Disorders[a] in Canada and New Zealand

		Canada				New Zealand		
Generic name (brand name)	**Clinical indication**	**Regulatory approval**	**Reimbursement recommendation**	**Price negotiation**	**Plans listing drug[b]**	**Regulatory approval**	**Available**	**Formulary listing**
Ivacaftor (Kalydeco)	Cystic fibrosis, G551D mutation	2012	Positive	Completed	8 (72.7%)	2013	No[c]	No
Ivacaftor (Kalydeco)	Cystic fibrosis, R117H and other gating mutations	2014	Positive	None	0 (0.0%)	2014	No[c]	No
Asfotase alfa (Strensiq)	Hypophosphatasia	2014	Positive	Completed	2 (18.2%)	-	No	No
Elosulfase alfa (Vimizim)	Mucopolysaccharidosis IVA	2014	Positive	Completed	1 (9.1%)	2015	Yes	No
Icatibant (Firazyr)	Hereditary angioedema	2014	Positive	Completed	10 (90.9%)	2015	Yes	Yes
Teduglutide (Revestive)	Short bowel syndrome	2015	Positive	Completed	5 (45.5%)	2019	No[c]	No
Nitisinone (Orfadin, MDK-Nitisinone, or Nitisinone)	Tyrosinemia type 1	2016	Positive	Completed	5 (45.5%)	-	No	No
Cysteamine (Procysbi)	Nephropathic cystinosis	2017	Positive	Completed	7 (63.6%)	-	No	No
Eliglustat (Cerdelga)	Gaucher's disease	2017	Positive	No agreement	0 (0.0%)	-	No	No
Migalastat (Galafold)	Fabry Disease	2017	Positive	Completed	4 (36.4%)	-	No	No
Nusinersen (Spinraza)	Spinal muscular atrophy	2017	Positive	Completed	7 (63.6%)	2018	No[c]	No
Eculizumab (Soliris)	Atypical hemolytic uremic syndrome	2013	Negative	No agreement	1 (9.1%)	-	No	No
Lomitapide (Juxtapid)	Homozygous familial hypercholesterolemia	2014	Negative	None	1 (9.1%)	-	No	No
Taliglucerase alfa (Elelyso)	Gaucher's disease	2014	Negative	Completed	4 (36.4%)	2017	Yes	Yes

[a]Drugs for disorders with prevalence of ≤2 per 100,000 with a price negotiation outcome in Canada reported between January 2014 and December 2018.
[b]As of December 31, 2019.
[c]Has regulatory approval but is unavailable in New Zealand.

TABLE 3. Approval and Reimbursement Status of Oncology Drugs for Ultra-Rare Disorders[a] in Canada and New Zealand

		Canada				New Zealand	
Generic name (brand name)	**Clinical indication**	**Regulatory approval**	**Reimbursement recommendation**	**Price negotiation**	**Plans listing drug[b]**	**Regulatory approval**	**Formulary listing**
Vandetanib (Caprelsa)	Medullary thyroid cancer	2012	Positive	Completed	6 (54.5%)	-	No
Regorafenib (Stivarga)	Gastrointestinal stromal tumor	2013	Positive	Completed	10 (90.9%)	2014	No
Romidepsin (Istodax)	Peripheral t-cell lymphoma	2013	Positive	Completed	9 (81.8%)	-	No
Siltuximab (Sylvant)	Castleman's disease	2014	Positive	Completed	5 (45.5%)	2015	Yes
Bosutinib (Bosulif)	Chronic myeloid leukemia	2014	Positive	Completed	9 (81.8%)	-	No
Ibrutinib (Imbruvica)	Mantle cell lymphoma	2014	Positive	Completed	10 (90.9%)	2015	No
Trabectedin (Yondelis)	Liposarcoma or leiomyosarcoma	2011	Negative	None	0 (0.0%)	-	No
Ibrutinib (Imbruvica)	Waldenstrom's macroglobulinemia	2016	Negative	None	1 (9.1%)	2016	No

[a]*Oncology drugs for disorders with prevalence of ≤2 per 100,000 with a price negotiation outcome in Canada reported between January 2014 and December 2018.*
[b]*As of December 31, 2019.*

regulatory approval in New Zealand than in Canada. Only a third of the rare disorder drugs with regulatory approval in New Zealand were listed in the Pharmaceutical Schedule. Both countries listed fewer DURDs, but with only two of the 14 DURDs listed in New Zealand, patient access to these drugs is considerably poorer than in Canada. Drugs not listed by PHARMAC are frequently made unavailable by the manufacturer.

The analysis is limited by the lack of information about rare disorder drugs covered by private insurance companies in Canada since their formularies are not publicly available. However, about two-thirds of Canadians have private insurance coverage, which generally has better coverage than public plans, whereas few New Zealanders have private drug insurance, which implies that differences in access between the two countries are more extreme than the results presented here indicate.

One reason that manufacturers seek regulatory approval in New Zealand later and for fewer products than in Canada could be New Zealand's smaller population (4.8 million compared with 37 million). Other reasons are how decisions are made about what new medicines will be listed (e.g., more expensive drugs may only be listed if they have much greater efficacy than older and cheaper drugs already listed) and who will have coverage (e.g., a drug may be restricted to a particular subset of patients with the disorder for which the drug is indicated), the degree to which prices are controlled, and how prices are negotiated.

Listing in the Pharmaceutical Schedule is tightly controlled. The province of Ontario's public drug plan formulary lists approximately 4,000 medicines,[23] while the Schedule lists about 2,000.[24] With few medicines listed in several drug classes, New Zealand patients and health care providers have limited therapeutic choices. However, humans are biologic entities and, as such, can vary widely in how effective a drug is and what adverse effects it can cause. Choices in a therapeutic class are essential. Furthermore, many of the listed medicines are older products.[25] For example, ambrisentan and bosentan, older drugs for pulmonary arterial hypertension, are listed in the Schedule and in nine of the 11 Canadian public drug plan formularies, but, unlike PHARMAC, most Canadian plans also list two newer pulmonary arterial hypertension drugs (riociguat and selexipag), which allows wider choice for combination therapy that is standard of care in this condition.[26] Newer drugs may not be more effective than older ones, but when they have fewer or less serious adverse effects and are easier to administer, adherence and persistency are improved, increasing the likelihood of a better outcome. Crucially for patients with rare disorders, many older drugs only treat their symptoms, whereas new drugs treat the actual disorder and offer longer life and improved quality of life.

PHARMAC works with a fixed annual budget and bargains tightly with manufacturers when assessing a new medicine for inclusion in the Pharmaceutical Schedule. It assesses and prioritizes new medicines against each other, taking account of drugs that must be forgone if a new one is listed, and against widened access to older drugs.[27] Price concessions must be obtained from manufacturers to fund a new medicine, and a drug is added to the Schedule only if an acceptable proposal is achieved, which can lead to "bundling" deals of multiple products from a manufacturer.[7] The result is more predictable pharmaceutical expenditures in New Zealand, but also relatively few new drugs being covered and an expanding list of new medicines that are acceptable but deferred,[28] including drugs for pulmonary arterial hypertension (e.g., macitentan and selexipag have been waiting for more than 4.2 and 3.2 years, respectively), idiopathic pulmonary fibrosis, Gaucher's disease, and phenylketonuria. This leads to manufacturers delaying seeking approval and reimbursement in New

Zealand or not taking their drugs there at all, as well as limiting investment in the country in terms of research and facilities.

In Canada, the PMPRB has set ceiling prices for new drugs for the past 30 years by comparing the price that a pharmaceutical manufacturer intends to charge against the highest and median international prices in seven countries: France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States. Under the new guidelines, the United States and Switzerland will be replaced by Australia, Belgium, Japan, the Netherlands, Norway, and Spain; and the intended Canadian price will have the lowest available list price in the 11 countries as the floor price and the median international price as the ceiling price, which will be used for both private and public payers. This will drive down prices by more than 20%.

In addition, the price may be further reduced based on a pharmacoeconomic evaluation of the medicine. Pharmacoeconomic analyses have previously been used to inform price negotiations between manufacturers and payers, not to set price ceilings. Their use in regulating prices is inappropriate because they are based on data and methods for which no standards exist and produce subjective, assumption-dependent assessments of uncertain validity. Pharmacoeconomic analyses will, nevertheless, be applied to calculate market-wide price ceilings that are definitive and legally enforceable and could be 45–84% below existing levels.[12]

Severe price reductions and the requirement that pharmaceutical manufacturers divulge information on confidential price rebates will drastically diminish the attractiveness of Canada as a country in which companies want to do business.[10–12] In a recent survey of pharmaceutical executives regarding the PMPRB changes,[29] all respondents believed that the changes would negatively effect their overall business plans in Canada and almost all responded that they would negatively impact product launches, commercialization and supply of current products (97%), employment (97%), and clinical research (91%) in Canada. This would result in access to all new medicines in Canada becoming like the situation in New Zealand, which has the potential to adversely effect the health of all Canadians irrespective of whether they have private or public drug coverage. For Canadians with rare disorders, life is already difficult – federal government actions should not make it worse.

CONFLICTS OF INTEREST

In the past 3 years, the author has received consultant fees from 3Sixty Public Affairs Inc and Fasken; research and publication fees from Advocacy Solutions, Bayer Inc, the Canadian Health Policy Institute, the Fraser Institute, Medicines New Zealand, Merck Sharp & Dohme (New Zealand) Ltd, RAREi (a collaboration of innovative pharmaceutical companies focused on the development of medicines for rare disorders, including Alexion Pharma Canada Corp, Amicus Therapeutics Canada Inc, Biogen Canada Inc, BioMarin Pharmaceutical Inc, Horizon Therapeutics Canada, Ipsen Biopharmaceuticals Canada Inc, Mitsubishi Tanabe Pharma Canada, Recordati Rare Diseases Canada Inc, Sobi Canada Inc, Ultragenyx Pharmaceutical Inc and Vertex Pharmaceuticals (Canada) Inc) and Ward Health; publication processing expenses from BIOTECanada, Canadian PKU and Allied Disorders Inc and Shire Pharma Canada ULC; and honorarium and compensation for travel from La Fondation DEVENIR. No conflict of interest exists between these activities and the present work.

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DATA AVAILABILITY STATEMENT

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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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