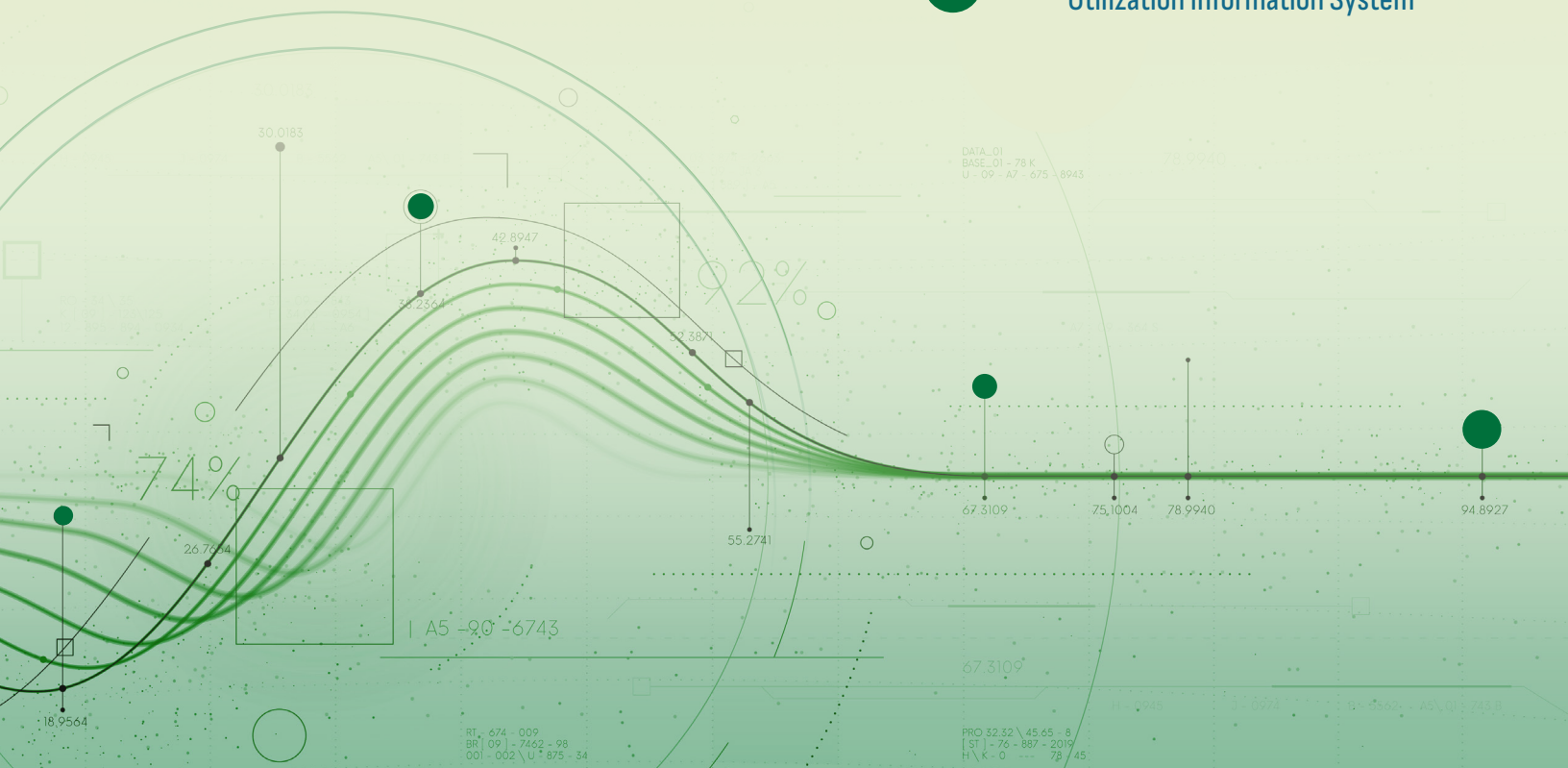
Patented Medicine Prices Review Board
Conseil d'examen du prix des médicaments brevetés
Canada

MARKET INTELLIGENCE REPORT

Antidiabetic Drugs 2012 • 2021

NPDUIS
National Prescription Drug Utilization Information System



About the PMPRB

The Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial body established by Parliament in 1987. The PMPRB has a dual regulatory and reporting mandate: to ensure that prices at which patentees sell their patented medicines in Canada are not excessive; and to report on pharmaceutical trends of all medicines and on research and development spending by patentees.

The NPDUIS Initiative

The National Prescription Drug Utilization Information System (NPDUIS) is a research initiative established by federal, provincial, and territorial Ministers of Health in September 2001. It is a partnership between the PMPRB and the Canadian Institute for Health Information (CIHI).

Pursuant to section 90 of the *Patent Act*, the PMPRB has the mandate to conduct analysis that provides decision makers with critical information and intelligence on price, utilization, and cost trends so that Canada's health care system has more comprehensive and accurate information on how medicines are being used and on sources of cost pressures.

The specific research priorities and methodologies for NPDUIS are established with the guidance of the NPDUIS Advisory Committee and reflect the priorities of the participating jurisdictions, as identified in the NPDUIS Research Agenda. The Advisory Committee is composed of representatives from public drug plans in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Yukon, the Non-Insured Health Benefits Program (NIHB), and Health Canada. It also includes observers from CIHI, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Canadian Drug Agency (CDA) Transition Office, the Ministère de la Santé et des Services sociaux du Québec (MSSS), and the pan-Canadian Pharmaceutical Alliance (pCPA) Office.

Acknowledgements

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Executive Summary

One hundred years ago in 1923, the Nobel Prize for Physiology or Medicine was awarded to Frederick Grant Banting and Professor John James Rickard Macleod for the discovery of insulin, a milestone in the treatment for diabetes that has saved countless lives. Today, diabetes remains a common cause of illness and shortened life expectancy, putting pressure on health care budgets. In 2021, Canada ranked 9th in diabetes prevalence among the Organization for Economic Co-operation and Development (OECD) member countries and 2nd among the PMPRB's 11 comparator countries. Diabetes will continue to be an ongoing concern for Canadian health care as the population ages.

This report explores the market dynamics affecting spending on antidiabetic drugs with an emphasis on new-generation/non-insulin drugs that experienced substantial growth over the course of the last decade. Trends in market shares and utilization are analysed at both the national and international levels. Foreign-to-Canadian price ratios and the impact of provincial biosimilar switching policies are also explored.

Key Findings

1 Antidiabetic drug growth outpaced the overall drug market

Growth in spending on antidiabetic drugs in Canada has continued to outpace spending in the overall drug market, effectively doubling the market share for these drugs from 4.2% to 7.9% (2012 to 2021). This growth reflects a shift to new classes of drugs for the treatment of diabetes resulting in a similar increase in the cost per capita for antidiabetic drugs from $26 to $71 (2012 to 2021). While OECD countries, particularly PMPRB11 comparators, faced similar spending trends and shifting utilization patterns, Canada ranked among those with higher costs and steeper increases.

2 New-generation treatments were the main driver of growth

In 2021, nearly three quarters (71%) of antidiabetic drug sales in Canada were for the new-generation/non-insulin subclasses. These drugs were responsible for almost all of Canada's increase in cost per capita of antidiabetic drugs since 2012. The uptake of new-generation/non-insulin treatments began in late 2007 with the launch of the first DPP-4, Januvia. After a strong early growth, spending on DPP-4's slowed following the launch of SGLT-2's in the mid-2010's suggesting a shift from DPP-4's to SGLT-2's. By 2021, DPP-4's and SGLT-2's accounted for 24% and 22% of spending on antidiabetic drugs, respectively. While GLP-1's had little impact on spending in the early 2010's, by 2021, GLP-1's accounted for 25% of all antidiabetic drug spending due to the substantial growth of semaglutide (Ozempic) launched in 2018. In addition to changing prescribing guidelines for antidiabetics, additional indications for the treatment of heart failure and weight management have contributed to the uptake of the new-generation/non-insulin drugs.

3 Canadian prices were higher than PMPRB11 countries

Canada has higher prices for top-selling antidiabetic drugs compared to prices in the PMPRB11 comparator countries, which were roughly half to two-thirds of Canadian prices in 2021. It is estimated that these higher prices could represent additional spending of up to $703M in Canada, all payers (public, private, cash) and segments (retail and hospital) combined. It is possible that some payers have already achieved savings through confidential pricing agreements, which are not reported in the data and list prices.

4 Biosimilar policies led to more switching

Drugs in the new-generation/non-insulin market in Canada were still patented during the study period and generic competition will be gradual as the first DPP-4's face competition in the future. Rather, during the study period, it is the biosimilars in the insulin market that offered opportunity for savings. A case study of insulin glargine (Lantus) showed a near-total switch to biosimilars in public plans in both British Columbia (by 2020) and Alberta (by 2021) following the implementation of a biosimilar switching policy affecting all patients, i.e., established and naïve (new) patients. Switching policies that target only naïve patients, in effect since 2017/18 in Quebec and Atlantic provinces, resulted in a significant, albeit smaller, shift to biosimilars by 2021 (53% to 80% biosimilars), outperforming provinces without biosimilar policies (5% to 23% biosimilars). The total market for insulin glargine (Lantus and biosimilars) was further affected by provincial plan formulary decisions such as removing reimbursement criteria for this class of insulins, and the decision to list insulin degludec (Tresiba), a new long-acting insulin. For example, in Alberta, the implementation of the biosimilar policy coincided with the listing of insulin degludec, which may have contributed to a 33% drop in total insulin glargine claims. Finally, market shares observed in private plans and in the cash market reflected the extent to which these segments operate in an integrated environment.

Table of Contents

Introduction

This report on antidiabetic drugs is part of the PMPRB's Market Intelligence Report series. These reports dive into specific therapeutic market segments that matter to Canadians. They use real-word evidence to inform policy discussions and support decision making while providing Canadians with an understanding of the issues that affect drug prices and utilization, both in Canada and internationally.

The Public Health Agency of Canada estimates the total number of individuals diagnosed with diabetes at over 3 million Canadians, representing an 8.9% prevalence rate. Furthermore, according to estimates by Diabetes Canada, the combined number of diagnosed and undiagnosed patients reached 5.7 million in 2022 and an additional 6 million Canadians are likely prediabetic. The cost burden of diabetes in Canada is estimated at $29 billion annually.[1] Type 1 diabetes is an autoimmune condition and represents roughly 10% of individuals living with diabetes. The risk of developing type 2 diabetes, however, is linked to common lifestyle factors such as diet, exercise, and smoking. Once diabetes is diagnosed, most patients will require antidiabetic drugs in addition to lifestyle changes to manage their condition. Over time other co-morbidities can surface leading to additional costs to health care systems and decreased quality of life and life expectancy for the patient.

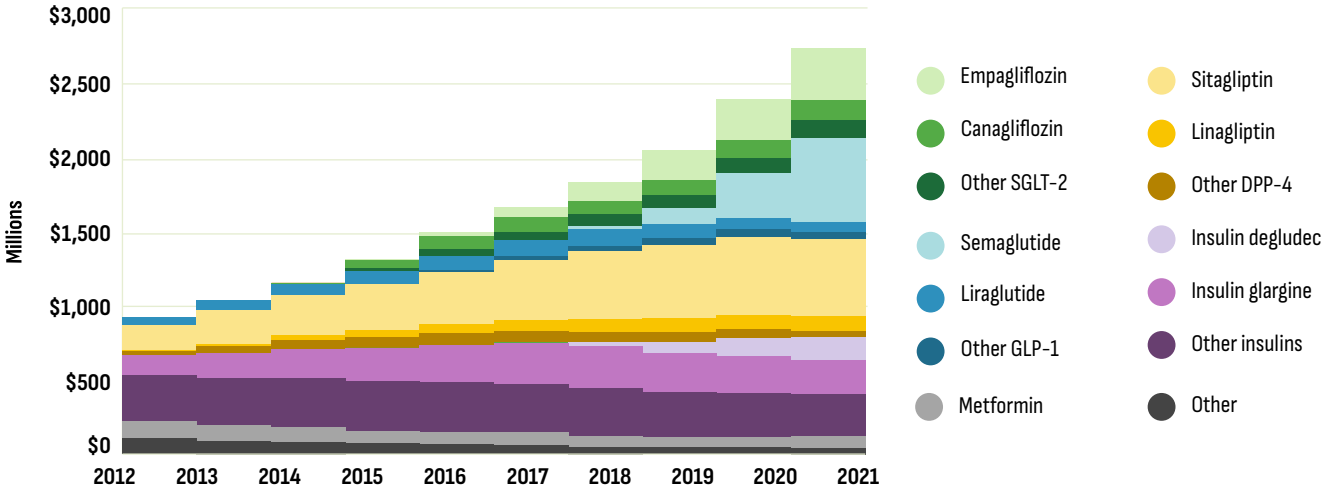
Spending on antidiabetic drugs in Canada increased substantially from $0.9 billion in 2012 to $2.7 billion in 2021 (see Figure I.1). This increase outpaced the growth in the overall drug market resulting in an increased market share for antidiabetic drugs from 4.9% (2012) to 7.9% (2021).

The three new-generation/non-insulin drug subclasses, which are the focus of this report, were the key drivers of this increase: glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase (DPP-4) inhibitors, and sodium glucose cotransporter 2 (SGLT-2) inhibitors. While insulin sales remained stable during this period, notable changes occurred in Canada: provincial drug plans implemented biosimilar switching policies and insulin degludec (Tresiba) entered the market.

These trends in market shares and underlying utilization patterns are explored throughout this report. Section 1 provides a primer on diabetes in Canada and looks at diagnosis, treatment, and prevalence. Section 2 provides an overview of the regulatory and reimbursement landscape, highlighting key decisions and advice from major agencies and regulatory bodies. Section 3 dives into the numbers and explores the PMPRB's real-world databases to reveal the cost drivers at play in this market. These include cost and utilization trends as well as international price comparisons and domestic competition. Finally, Section 4 looks at what the future may hold for new drugs in the pipeline for the treatment of diabetes.

Figure I.1

Canadian sales for antidiabetic drugs (2012-2021)



Note: Sales for each molecule include sales for versions in combination with metformin. For example, sales of empagliflozin include both sales for empagliflozin alone (Jardiance) and empagliflozin and metformin (Synjardy).

Data source: IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022). All rights reserved.

Methods

Drug selection

Antidiabetic drugs were selected at level 4 of the World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) classification system in the A10A (insulin) and A10B (non-insulin) categories (see Table M1). Devices were excluded. While diabetes is the primary indication for these drugs, some have other indications such as drugs in the SGLT-2 class that are also indicated for heart failure. The databases analyzed do not include information on the patient's diagnosis and consequently it is not possible to determine with certainty the indication for which a drug is prescribed.

Table M1

Antidiabetic drugs included in analysis, by subclass

Subclass	ATC	Molecules
SGLT-2: sodium-glucose cotransporter-2 inhibitors. Oral solid medications that block the reabsorption of glucose in the kidney, thereby increasing the amount of glucose excreted through the urine.	A10BK A10BD	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and their combinations with metformin or with DPP-4's. Combinations with insulins are grouped with insulins.
GLP-1: glucagon-like peptide-1 receptor agonists. Primarily injectable pens that stimulate the release of insulin and reduce the release of glucagon from the pancreas.	A10BJ	Semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide.
DPP-4: dipeptidyl peptidase-4 inhibitors. Oral solid medications that stimulate the release of insulin when blood glucose is rising and inhibit the release of glucose from the liver.	A10BH A10BD	Sitagliptin, saxagliptin, linagliptin, alogliptin, and their combinations with metformin. Combinations with SGLT-2 are grouped with SGLT-2.
Insulins: All forms of insulin (injectables).	A10A A10AE	Featured analysis looks at insulin glargine and insulin degludec in the subclass of long-acting soluble basal insulin analogue (A10AE).
Metformin: Biguanides.	A10BA	All sources of metformin not in combination with other molecules.
Other	A10BB A10BF A10BG A10BX	Sulfonylureas Alpha glucosidase inhibitors Thiazolidinediones Other blood glucose lowering drugs, excluding insulins.

Comparator countries

This report compares Canada to members of the Organization for Economic Co-operation and Development (OECD), and specifically focuses on the PMPRB's new basket of 11 comparator countries (PMPRB11): Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, Spain, Sweden, and the United Kingdom (UK). When appropriate, the United States (US) and Switzerland are included as they were both in the original PMPRB basket of 7 countries (PMPRB7). For reference, countries are labelled in the figures with 7 and/or 11 to indicate their inclusion in the current PMPRB11 basket and the PMPRB7 historical basket (e.g., France (7/11)).

Data sources

The findings in this report are based on an analysis of databases from IQVIA and the National Prescription Drug Utilization Information System (NPDUIS) database managed by the Canadian Institute for Health Information (CIHI). These are detailed below along with notes on notable considerations. Further descriptions of PMPRB source materials can be found in the Reference Documents section of the Analytical Studies page on the PMPRB website. Additional databases and resources consulted are listed below.

Drug sales and drug plan databases

NPDUIS	Provincial drug plan administrative data for all provinces except Quebec. Quebec public plan data provided in the report are estimates calculated using the IQVIA Payer Insights database (see below).
IQVIA MIDAS® Database (all rights reserved)	Country-specific international data for both retail and hospital sales. It includes units sold and sales amounts. These data are the primary source for international trends and price comparisons in Sections 3.1 and 3.2.
IQVIA Private Drug Plan database	Private drug plan administrative data obtained from pay-direct private insurers. While each supplier's data are complete, not all Canadian insurers are included in this database and coverage varies across provinces.
IQVIA Payer Insights database	Database generated from a sampling of retail (community) pharmacies that specifies first payer: public plan, private plan, or out-of-pocket (cash). Used mainly to calculate market shares for each payer (public/private/cash). Also used as a proxy to analyze drug utilization in the Quebec public drug plan (data not included in the NPDUIS database). These estimates are provided for market shares only where additional context is relevant.

Additional databases and online resources

- Information on provincial drug programs and formularies consulted online through their respective websites.
- Public Health Agency of Canada. Canadian Chronic Disease Surveillance System (CCDSS), Data Tool 2000–2017, 2019 Edition. Ottawa (ON): Public Health Agency of Canada; 2021. Available at: Canadian Chronic Disease Surveillance System (CCDSS) (canada.ca)
- Health Canada. Notice of Compliance Database. Government of Canada. Retrieved from: Notice of Compliance - Drug Products - Canada.ca.
- Statistics Canada. Table 11-10-0190-01 Market income, government transfers, total income, income tax and after-tax income by economic family type.
- World Health Organization. A10AE Insulins and analogues for injection, long-acting. Available at: WHOCC - ATC/DDD Index.
- Organisation for Economic Co-operation and Development. Dataset: Historical Population. Available at: https://stats.oecd.org/.
- pan-Canadian Pharmaceutical Alliance. Brand Name Drug Negotiations. Available at: https://www.pcpacanada.ca/negotiations
- GlobalData Healthcare database

Data limitations

Sales and spending reported in the drug sales and drug plan databases listed do not capture confidential price discounts. Price differentials and expenditure values may be overestimated or underestimated depending on these discounts in both Canadian and foreign markets.

In addition, drug plan databases do not contain information on the reason a drug is prescribed. While most antidiabetic drugs are prescribed for treating diabetes, some drug classes may be used for other indications (see: Drug selection, above).

1 Diabetes Backgrounder

This section provides key information on the causes, diagnosis, and drug therapies for diabetes as well as the current prevalence and incidence of diabetes in Canada.

1.1 About diabetes mellitus: definition, diagnosis, and treatment

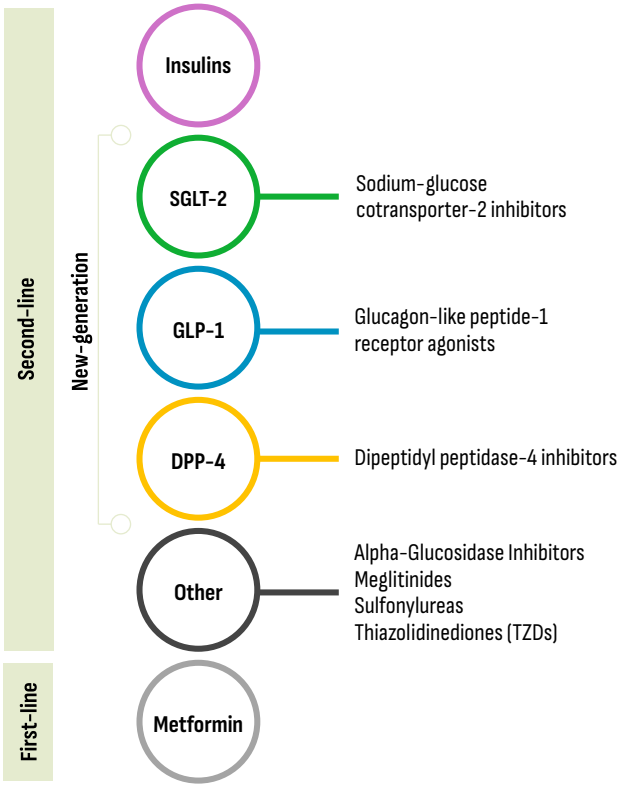
Diabetes mellitus is a chronic condition associated with impairment of insulin secretion. Insulin is a hormone produced by the pancreas and is essential for regulating blood glucose (sugar) levels. Diabetes occurs when insulin levels are insufficient or when the body responds poorly to the insulin produced (insulin resistance). The goal of diabetes treatment is to regulate blood glucose to a healthy level. It is diagnosed and monitored by measuring the amount of glucose present in the patient's bloodstream. Poorly regulated glucose levels can lead to major complications such as heart disease, vision loss, and kidney disease.

Diabetes falls predominantly under two types.[i] **Type 1 diabetes** is an autoimmune condition where the immune system destroys the insulin-producing cells found in the pancreas which can no longer produce sufficient insulin. It is usually diagnosed in childhood. There is no known cure and daily insulin injections are currently the only treatment option. In **type 2 diabetes**, the body is either unable to process insulin effectively or the pancreas does not produce enough insulin. It is considered preventable given its strong link to lifestyle risk factors (diet, activity, smoking), but there are other non-modifiable risk factors at play such as genetic predisposition and ethnicity. It is a condition that develops gradually over time and is primarily diagnosed in adults. However, recent years have seen an increase of the disease in adolescents and children, although they remain a very small proportion of overall cases.

Drug treatment for type 2 diabetes can be complex with many non-insulin drug options (see Figure 1.1 and Methods section for a detailed list). These may be prescribed as monotherapy or as various combination drug regimens. Metformin is generally considered the **first-line** choice for people with type 2 diabetes because of its safety, low cost, and possible heart benefits.[2] If optimal glucose levels are not reached, and prior to introducing insulin, a variety of **second-line** therapies are considered. Of these possible second-line therapies, the DPP-4's, GLP-1's, and SGLT-2's are relatively recent additions (see Section 2) and are referred to as "new-generation/non-insulin" drugs throughout this report.

Drug treatments are tailored according to each patient's unique circumstances considering overall health, age, severity of disease, as well as the presence of co-morbidities such as heart disease and kidney function. In addition, the management of the overall drug load for patients with multiple chronic conditions presents unique challenges related to possible drug interactions and treatment adherence. This affects the dosing schedule and the choice of oral versus injectable forms. Only insulins and most GLP-1's are injectable drugs. The remainder of antidiabetic drugs are oral solids. Semaglutide is the only GLP-1 sold as both an injectable (Ozempic) and an oral option (Rybelsus).

Figure 1.1
Type 2 diabetes drug treatment



i Additional categories include prediabetes and gestational diabetes. Prediabetes is diagnosed when blood sugar levels are higher than normal but below the clinical threshold for diabetes. It is a reversable condition in some patients provided that effective lifestyle modifications are implemented. Gestational diabetes occurs during pregnancy and glucose levels usually return to normal post-delivery. Some may require insulin during pregnancy. There are also other rare types of diabetes related to genetic conditions, other diseases, and drug use.[3,4]

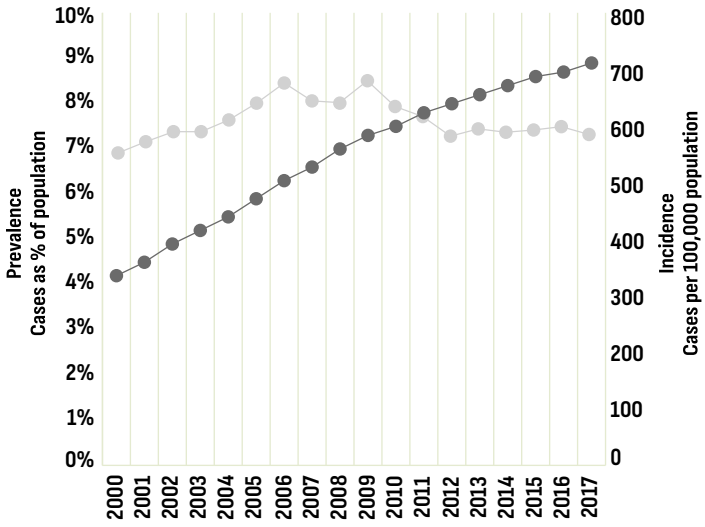
1.2 Diabetes prevalence and incidence

The Public Health Agency of Canada (PHAC) estimates that 8.9% of Canadians have been diagnosed with diabetes (over 3 million Canadians). Type 2 diabetes accounts for most cases (90%) followed by type 1 diabetes (9%) and gestational diabetes (1%). In addition, it estimates that 6.1% of adults (age 20 to 79) have prediabetes. PHAC provides data on incidence and prevalence of diabetes through the Canadian Chronic Disease Surveillance System (CCDSS).

The data reported are for type 1 and type 2 diabetes combined and exclude gestational diabetes. As shown in Figure 1.2, diabetes prevalence has been steadily increasing over the past decades despite a slight drop in incidence. These trends may appear contradictory; however, improved treatment can increase survival, thus increasing the number of individuals living with diabetes in a given year.

Figure 1.2

Prevalence vs. incidence rates for diabetes (type 1 and type 2)



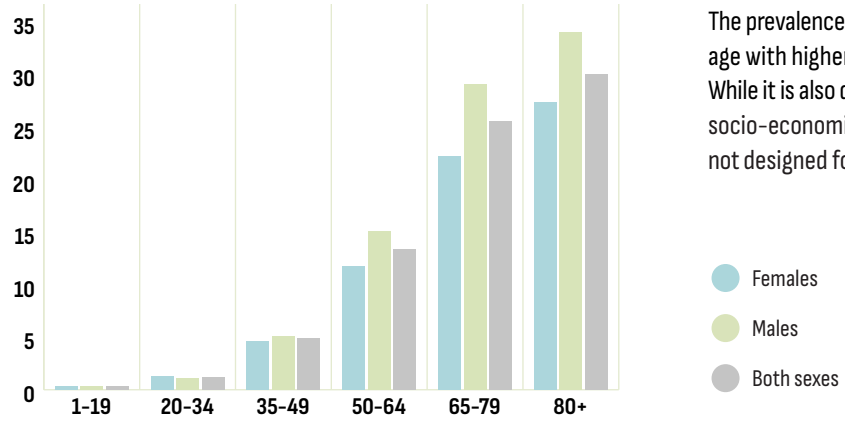
Prevalence: The total number of individuals with diabetes in a given year in a population, expressed as a proportion of that population (e.g., percentage).

Incidence: The number of newly diagnosed patients with diabetes in a given year in a population, expressed as a rate (e.g., cases per 100,000 people).

Source: Public Health Agency of Canada, Canadian Chronic Disease Surveillance System (CCDSS)

Figure 1.3

Diabetes prevalence by age and gender, 2017



The prevalence of diabetes (type 1 and type 2 combined) increases with age with higher rates for males compared to females (see Figure 1.3). While it is also documented that the prevalence varies by ethnicity and socio-economic factors, current drug plan information systems are not designed for reporting these patient characteristics.

Source: Public Health Agency of Canada, Canadian Chronic Disease Surveillance System (CCDSS)

2 Canada's Regulatory and Reimbursement Landscape

This section situates new antidiabetic drugs within the Canadian regulatory and reimbursement landscape, beginning with the launch of the first new-generation/non-insulin drug sitagliptin (Januvia) in late 2007. The section begins with a timeline outlining the entry of the first brand of each drug. This is followed by an overview of the PMPRB's classification of these drugs. The section ends with highlights of the advice from economic assessments and provincial negotiations and listing decisions.

The text box *Canadian Regulatory and Reimbursement Organizations* describes the organizations involved in making drugs accessible to Canadians. Appendix B provides details on the decisions and advice by these organizations for all the drugs selected for this report.

Canadian Regulatory & Reimbursement Organizations

Approval for Sale in Canada

Health Canada authorizes the marketing of drugs based on an assessment of the drug's safety and efficacy, as well as the quality of the manufacturing process for the drug. Health Canada issues the Notice of Compliance (NOC) and the unique Drug Identification Number (DIN).

Pricing

Patented: The **Patented Medicine Prices Review Board (PMPRB)** is an independent, quasi-judicial body mandated to protect consumers by ensuring that the prices of patented medicines are not excessive. The PMPRB does not set prices. It calculates the maximum (ceiling) price at which a company can sell the drug in Canada based on the assessment conducted by the HDAP.

The PMPRB convenes the **Human Drug Advisory Panel (HDAP)** to conduct scientific evaluations of new patented medicines. Criteria evaluated may include the level of therapeutic improvement, the drug's primary use, the selection of medicines to be used for comparison purposes, and comparable dosage regimens. The HDAP makes recommendations for the classification of new patented medicines into four possible "Therapeutic Criteria Levels" that reflect the drug's degree of innovation and therapeutic improvements compared to other drugs in Canada and which will determine the price ceiling applied.

Non-patented: Non-patented drugs are either originator products no longer patented or their competitors (generic or biosimilar alternatives).

Prices are not subject to regulatory requirements but formulary listings may depend on drug plan rules.

Economic Evaluations

Canada, except Quebec: The **Canadian Agency for Drugs and Technologies in Health (CADTH)** convenes the **Canadian Drug Expert Committee (CDEC)** to conduct evaluations of new and existing drugs regarding their clinical outcomes, economic costs, and patient impact. Evaluations are used to provide reimbursement recommendations and advice to public drug plans across Canada (federal/provincial/territorial), except Quebec.

Quebec: The **Institut national 'excellence en santé et en services sociaux (INESSS)** evaluates new and existing drugs and health technologies to issue recommendations for coverage by the Quebec public plan (Régime d'assurance-maladie du Québec). In addition, it develops related clinical practice guidelines.

Public Drug Plan Reimbursement (Formulary Listings)

The **pan-Canadian Pharmaceutical Alliance (pCPA)** conducts joint provincial/territorial negotiations for brand name and generic drugs in Canada to achieve greater value for publicly funded drug programs and patients. The outcome of these negotiations can have a determining impact on the decision to list a drug.

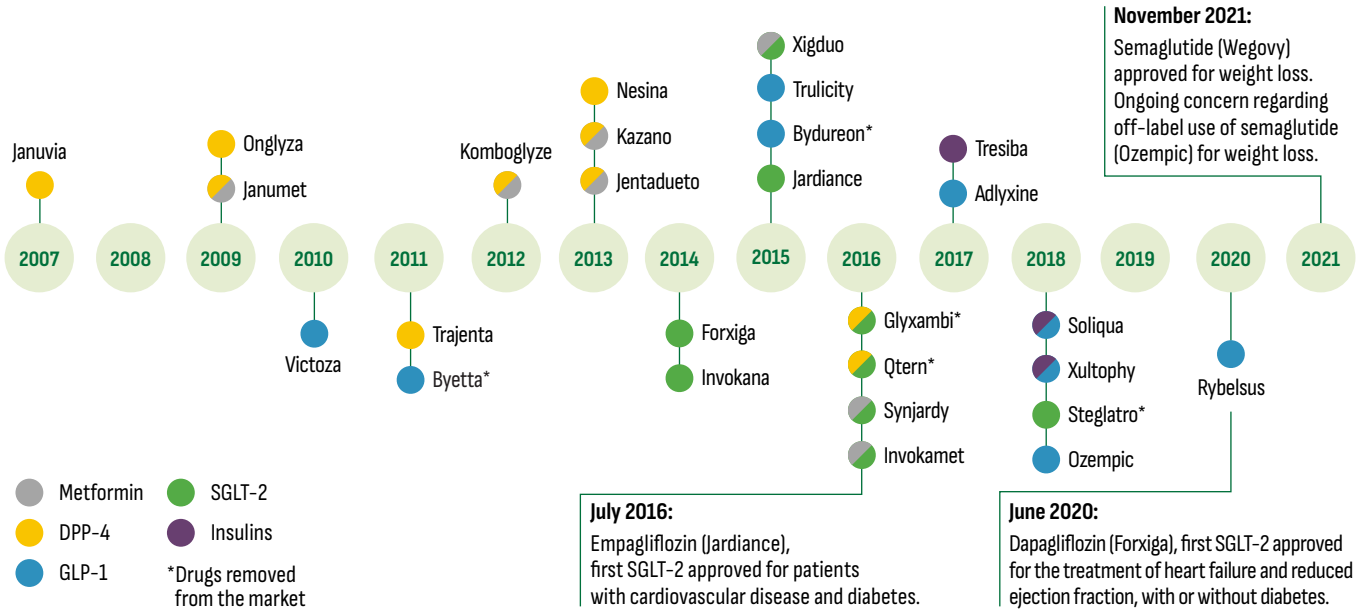
Each **provincial public drug plan** makes their final formulary listing decisions based on the advice from the above organizations and other factors specific to their province such as legal mandates, health care priorities, and budget impact.

Figure 2.1 illustrates the timeline of the allocation of the first Notice of Compliance (NOC) by Health Canada for each new antidiabetic drug, beginning in 2007 with sitagliptin (Januvia), the first DPP-4. For simplicity, only brand names are provided in the figure.

While all drugs shown in Figure 2.1 are indicated for diabetes, some acquired indications for other conditions or may be used off-label. The figure indicates instances where utilization may be significantly impacted and attributable to indications other than diabetes. Finally, except for insulin degludec (Tresiba), all drugs shown in Figure 2.1 are currently patented medicines.[ii]

Figure 2.1

Health Canada market approvals: first Notice of Compliance and notable indications



The PMPRB's Human Drug Advisory Panel (HDAP) provides recommendations for the categorization of new products and the selection of comparable drug products.[iii] Sitagliptin (Januvia) was not only the first **DPP-4**, but also the first new-generation/non-insulin product. It was classified as a Category 3 medicine (moderate, little or no therapeutic advantage) according to the guidelines in effect at the time. The HDAP compared Januvia to existing classes (α-glucosidase inhibitors, meglitinides, thiazolidinediones, and sulfonylureas) because there were no comparators within the same 4th level ATC class. Subsequent DPP-4's and their metformin combinations received similar designations. Liraglutide (Victoza) was the first **GLP-1** and was also classified as a Category 3 medicine. The HDAP recommended insulin glargine (Lantus) as the most appropriate comparator, stating that both would be prescribed similarly as second- or third-line therapy despite not sharing the same 4th level ATC class and despite the availability of DPP-4's. Subsequent GLP-1 and insulin combinations and all **SGLT-2**'s (beginning with canagliflozin (Invokana) in 2014) were similarly classified as "slight or no therapeutic improvement" under the new (2010) guidelines. The HDAP included DPP-4's and other oral agents as comparators in their evaluation of SGLT-2's.

The initial review by the CADTH Canadian Drug Expert Committee (CDEC) of the first DPP-4 drugs (Januvia and Onglyza) resulted in a recommendation to provincial drugs plans to not list these drugs. By 2012, the beginning of the period analyzed in this report, the CDEC's recommendation for all DPP-4's was reimbursement with criteria (e.g., limited use). It then continued with this advice for all subsequent new-generation/non-insulin drugs including combination drugs with insulin (Soliqua, Xultophy) as well as insulin degludec (Tresiba). These reimbursement criteria consider failure on alternate therapies and contraindications (such as kidney function, heart-related risk factors, or inadequate blood glucose control on alternate drugs, typically metformin and/or sulfonylurea).[5]

For the most part, provinces followed CADTH's advice and listed DPP-4's and SGLT-2's with limited criteria, except for Ontario, which listed these drugs as open benefits. The two GLP-1's, Adlyxine and Ozempic, were listed as full benefits in Ontario and with criteria in Alberta, Saskatchewan, and New Brunswick. No province listed Rybelsus. All provinces except British Columbia listed Tresiba as a full benefit. For the new combination GLP-1/insulin drugs, no province listed Xultophy and Soliqua was listed as a full benefit in Ontario and with criteria in Saskatchewan.[6]

ii The patent for insulin degludec (Tresiba) lapsed in July 2017, one month before obtaining an NOC in August 2017.

iii Category recommendations prior to 2010 are available at: http://www.pmprb-cepmb.gc.ca/CMFiles/comp08-e38NBY-3182008-1638.pdf

3 Cost Drivers

Spending on antidiabetic drugs varies based on drug prices and utilization. Drug utilization, in turn, depends on factors discussed in Sections 1 and 2, such as drug options, drug access, and disease prevalence. Subsection 3.1 compares Canadian prices for a sample of top-selling antidiabetic drugs to the prices in the current PMPRB basket of 11 countries (PMPRB11), the former basket of 7 countries (PMPRB7), and across the OECD countries. Subsection 3.2 situates Canadian market trends among its international peers. Subsection 3.3 provides an extensive analysis of public (provincial) and private payers in Canada.

3.1 International price comparison

International prices are compared by calculating the ratio of the foreign price divided by the Canadian price[iv]. For each ratio, the Canadian price is set to one and the corresponding foreign prices are determined to be either higher than (above) or lower than (below) this level. The average price ratios are calculated using sales-weighted arithmetic means of price ratios obtained for the top-selling drugs in the DPP-4, SGLT-2, and GLP-1 subclasses. This ratio was also calculated for insulin degludec (Tresiba), the only new insulin product launched in Canada over the last decade. It is worth noting that insulin degludec was never subject to PMPRB reporting due its patent lapsing before receiving its NOC (see Section 2).

Figure 3.1 reports foreign-to-Canadian price ratios in 2021 for the PMPRB11 countries as well as Switzerland and the United States, which were part of the PMPRB7 list of comparator countries. The median for the PMPRB11, the PMPRB7, and OECD countries are provided at the bottom of each graph. The prices of the selected products in the PMPRB11 countries were 30% to 50% lower than the Canadian prices. Italy was most often second to Canada with ratios ranging from 0.59 for the DPP-4's to 0.77 for the GLP-1's and insulin degludec. The median PMPRB11-to-Canadian price ratio was 0.50 for DPP-4's, 0.69 for SGLT-2's, 0.61 for GLP-1's, and 0.60 for insulin degludec. The OECD-to-Canadian price ratio followed a similar trend.

Top-selling drugs selected for price comparison

DPP-4

- Sitagliptin (Januvia/Janumet*)
- Linagliptin (Tradjenta/Jentadueto*)

SGLT-2

- Canagliflozin (Invokana)
- Empagliflozin (Jardiance)

GLP-1

- Semaglutide (Ozempic)
- Liraglutide (Victoza)

Insulins

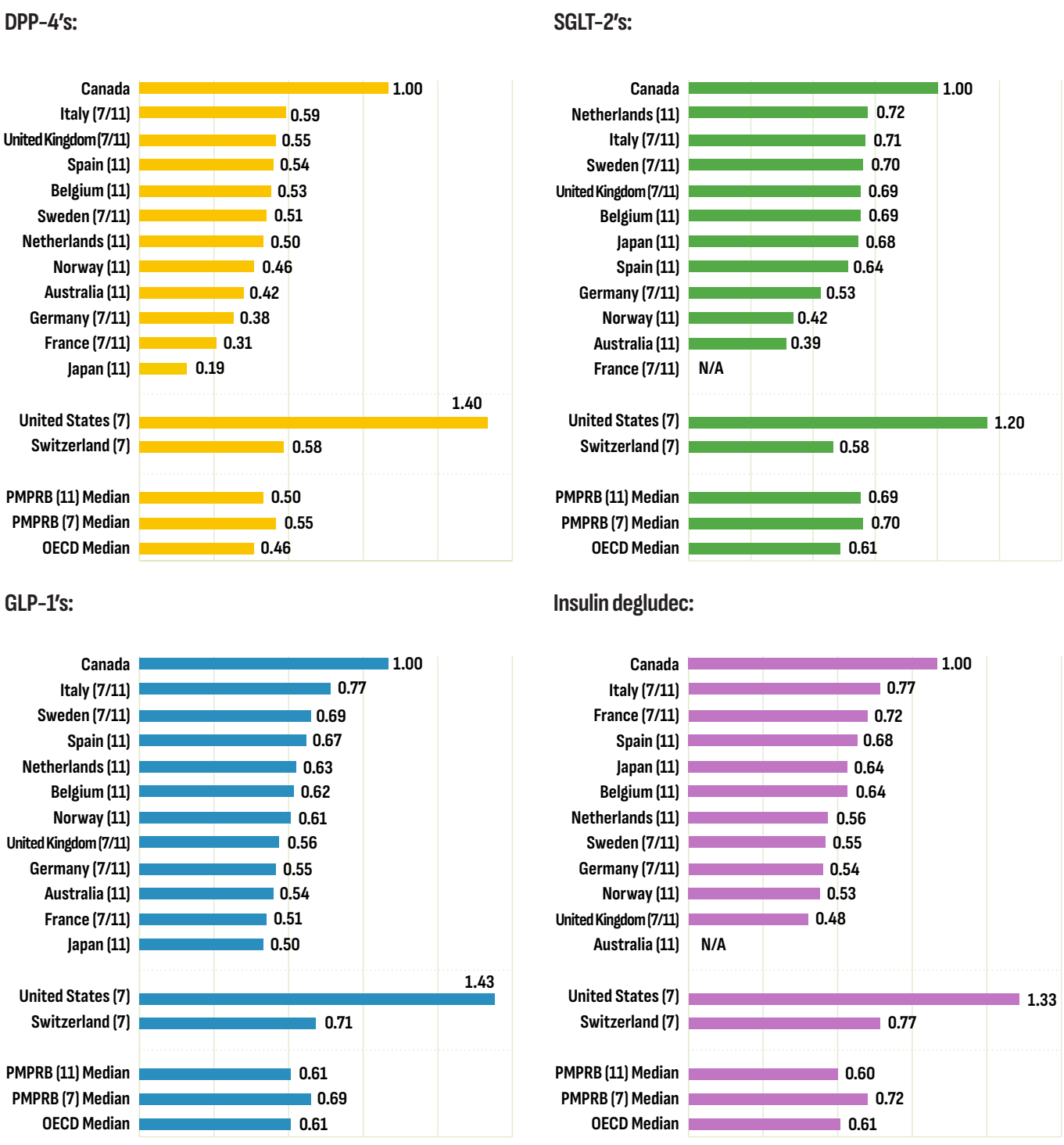
- Insulin degludec (Tresiba)

** Janumet and Jentadueto are the related ingredient combinations with metformin.*

iv These price comparisons are based on sales data from IQVIA MIDAS®. Estimates have been converted to Canadian dollar equivalents at annual average market exchange rates. For a more detailed description of how the foreign-to-Canadian price ratios are calculated, see the the Reference Documents section of the Analytical Studies page on the PMPRB website.

Figure 3.1

Average foreign-to-Canadian price ratios, top-selling DPP-4's, SGLT-2's, GLP-1's and insulin, Canada versus PMPRB11 median, PMPRB7 median, and OECD median, 2021



Data source: IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022). All rights reserved.

3.2 International markets

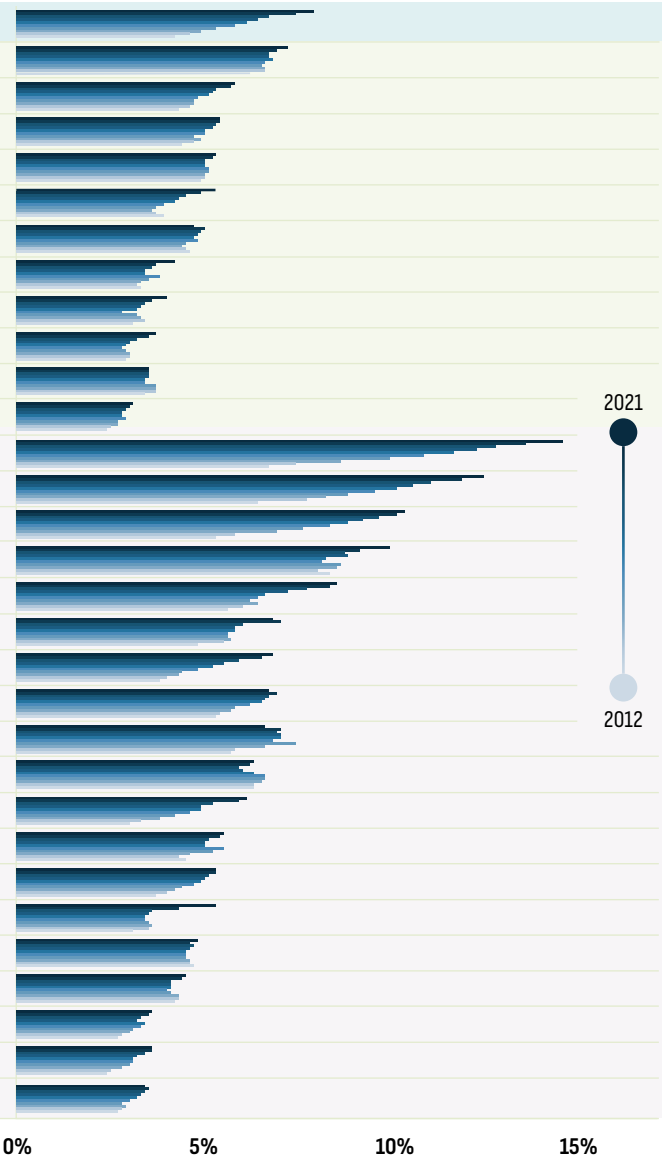
Sales of antidiabetic drugs in all OECD countries have outpaced sales growth in the overall drug market, resulting in a growth in market share for antidiabetic drugs over the last decade (see Figure 3.2). This growth in market share was predominantly the result of the increased utilization of new-generation/non-insulin drugs. International market share comparisons in any given year have limitations due to market-specific factors in each country. However, the overall level and growth of these market shares are indicative of shared challenges in diabetes management.

The Canadian market share for antidiabetic drugs relative to the overall drug market in 2021 (7.9%) was the highest among the PMPRB11, almost doubling from 2012 (4.2%). While the PMPRB11 countries also saw an increase in share since 2012, the growth in spending for antidiabetic drugs was more in line with the general growth of their respective domestic drug markets. For the PMPRB11 countries, the market share increase during this period was comparatively modest. Outside the PMPRB11, the US stood out among OECD countries with the highest market share for antidiabetic drugs in 2021 (14.5%) nearly doubling from its already significant share in 2012 (6.7%). Greece came in second with a 12.4% share in 2021.

Figure 3.2

Antidiabetic drug share of total market sales, 2012 to 2021

Country	2012	2017	2021
Canada	4.2%	6.1%	7.9%
Netherlands (11)	6.2%	6.8%	7.2%
Japan (11)	4.3%	5.1%	5.8%
Spain (11)	4.4%	5.0%	5.4%
Germany (7/11)	4.9%	5.0%	5.3%
Sweden (7/11)	3.9%	4.2%	5.3%
United Kingdom (7/11)	4.6%	4.7%	4.7%
Norway (11)	3.3%	3.4%	4.2%
Australia (11)	3.1%	3.2%	4.0%
Italy (7/11)	2.9%	2.9%	3.7%
France (7/11)	3.4%	3.4%	3.5%
Belgium (11)	2.4%	2.8%	3.1%
United States (7)	6.7%	11.6%	14.5%
Greece	6.4%	10.1%	12.4%
Luxembourg	5.3%	8.8%	10.3%
Estonia	8.3%	8.2%	9.9%
Portugal	5.6%	6.6%	8.5%
Turkey	4.8%	5.8%	6.8%
Mexico	3.8%	5.2%	6.8%
Hungary	5.3%	6.5%	6.7%
Czech	5.7%	7.0%	6.6%
Finland	6.3%	6.3%	6.3%
Chile	3.0%	4.9%	6.1%
Slovakia	4.5%	5.0%	5.5%
Korea	3.7%	4.9%	5.3%
New Zealand	3.1%	3.4%	5.3%
Slovenia	4.7%	4.5%	4.8%
Poland	4.2%	4.1%	4.5%
Switzerland (7)	2.7%	3.4%	3.6%
Ireland	2.4%	3.1%	3.6%
Austria	2.7%	3.2%	3.4%



Data source: IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022). All rights reserved.

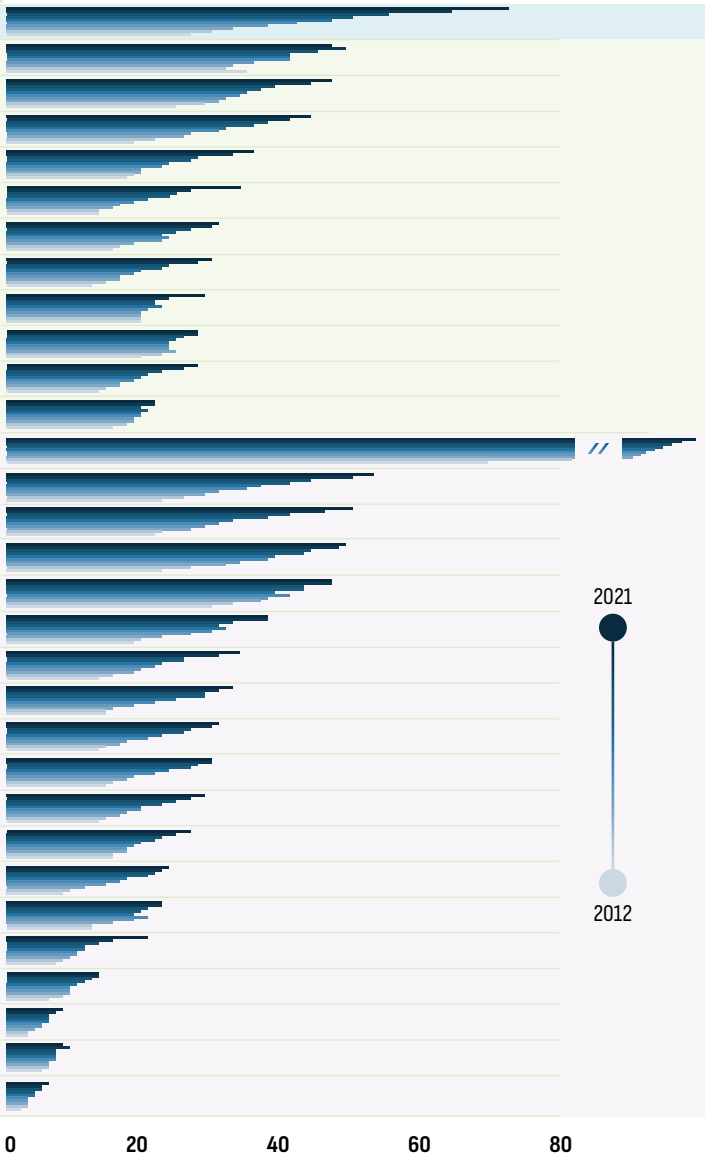
The cost increases resulted in cost per capita increases over the same period, most notably in the latter years. In 2021, Canada had the highest cost per capita ($71) of the PMPRB11, ahead of Japan ($46), Germany ($46), and Spain ($43) (Figure 3.3).

Among OECD countries, Canada was a distant second to the US ($316) but ahead of the next highest countries beginning with Greece ($52) and was more than double the median for both the OECD ($30) and PMPRB11 ($30).

Figure 3.3

Cost per capita, antidiabetic drugs, OECD countries, 2012 to 2021 (CAD)

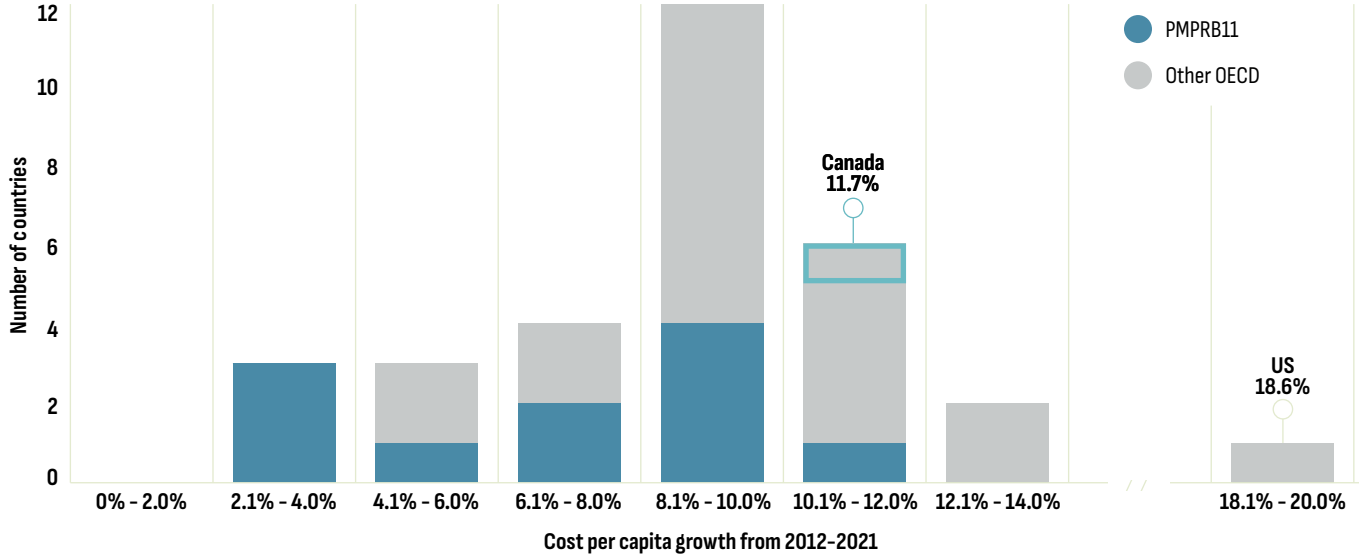
Country	2012	2017	2021
Canada	$26	$46	$71
Japan (11)	$34	$40	$46
Germany (7/11)	$24	$34	$46
Spain (11)	$18	$31	$43
Sweden (7/11)	$17	$23	$35
Norway (11)	$13	$20	$33
United Kingdom (7/11)	$15	$22	$30
Italy (7/11)	$12	$19	$29
Australia (11)	$19	$22	$28
France (7/11)	$19	$23	$27
Belgium (11)	$13	$19	$27
Netherlands (11)	$15	$19	$21
United States (7)	$68	$209	$316
Greece	$22	$36	$52
Portugal	$21	$32	$49
Luxembourg	$22	$38	$48
Finland	$29	$38	$46
Switzerland (7)	$18	$31	$37
Estonia	$13	$22	$33
Czech	$14	$24	$32
Austria	$13	$22	$30
Hungary	$14	$23	$29
Ireland	$13	$19	$28
Slovenia	$15	$19	$26
Korea	$8	$17	$23
Slovakia	$12	$18	$22
New Zealand	$7	$11	$20
Poland	$6	$10	$13
Chile	$3	$6	$8
Turkey	$5	$7	$8
Mexico	$2	$4	$6



Data sources: Organisation for Economic Co-operation and Development; IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022).

Figure 3.4

Distribution of percent increase in cost per capita, antidiabetic drugs, OECD countries, 2012-2021



CAGR: Compound annual growth rate

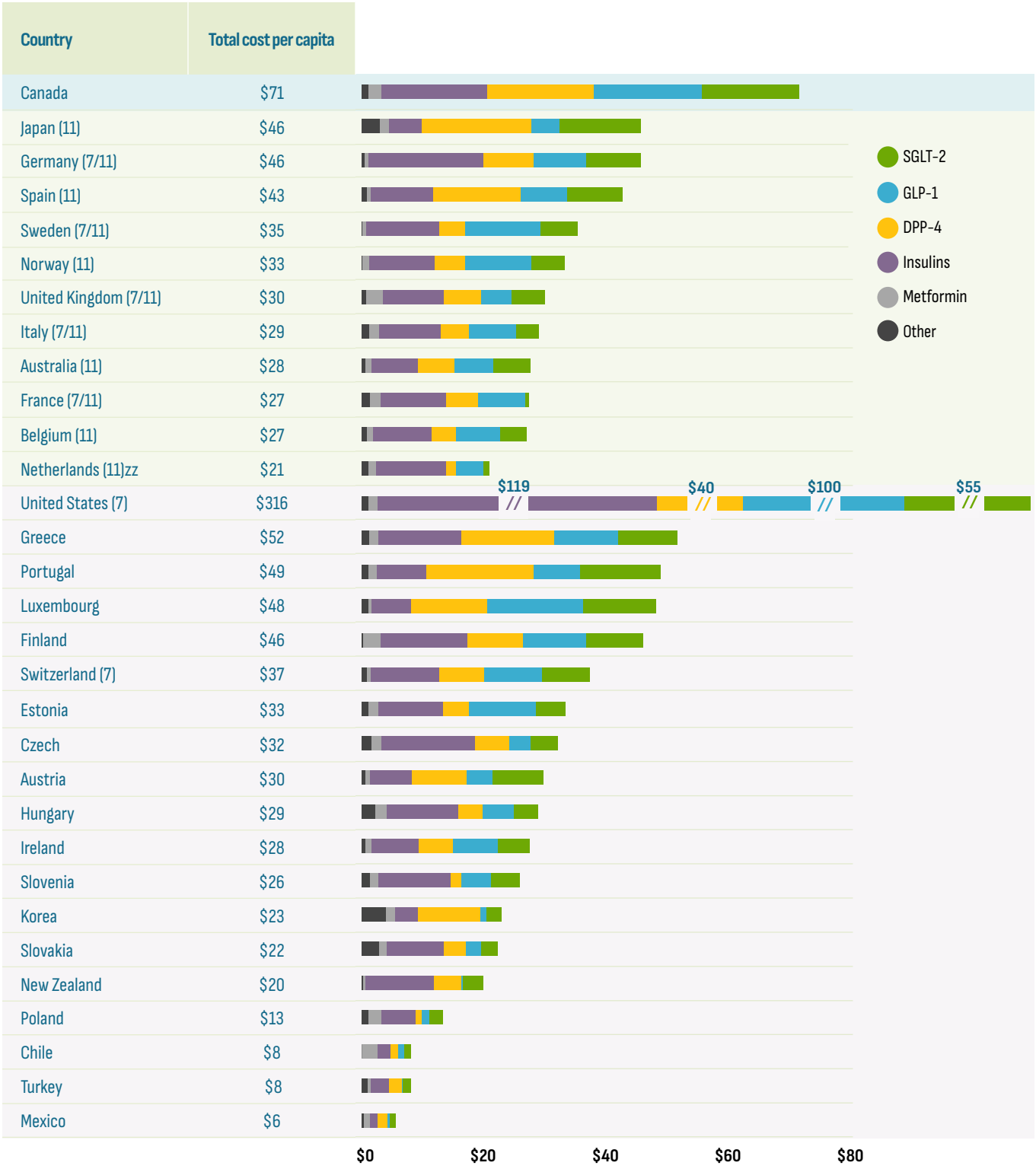
Data sources: Organisation for Economic Co-operation and Development; IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022).

While the cost per capita increased in all OECD countries (Figure 3.3), the key difference among countries is the size of this increase. Figure 3.4 shows the distribution of all OECD countries according to their respective percent increase in cost per capita since 2012. Each category on the horizontal axis displays a compound annual growth rate (CAGR) range in cost per capita from the smallest change observed (0% to 2.0%) to the largest (18.1% to 20.0%). Three PMPRB11 countries experienced increases below 4% in cost per capita: Japan (3.5%); the Netherlands (3.6%); and France (3.9%). An 8% CAGR represents a doubling in the cost per capita over this period and four countries were in this range: the UK (7.6%); Sweden (8.2%); Hungary (8.4%); and Switzerland (8.4%). Overall, two-thirds of countries had increase over 8%, including Canada (11.7%). The PMPRB11 was split with 5 countries below 8% and 6 above while other OECD more often saw increases above 8% (15 versus 4 countries).

Growth in cost per capita, regardless of scale, was driven by shifts in prescribing toward the new-generation/non-insulin drugs as further detailed below. It is also worth noting that the US experienced substantial increases in insulin prices over the last decade, particularly in the first half. Figure 3.5 divides the 2021 cost per capita by subclass. While the overall cost per capita varies across countries, the subclass distributions are similar and illustrate the relative importance of the new-generation/non-insulin subclasses (DPP-4, GLP-1, SGLT-2).

Figure 3.5

Cost per capita by antidiabetic drug subclass, OECD countries, 2021 (CAD)



Data sources: Organisation for Economic Co-operation and Development; IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022).

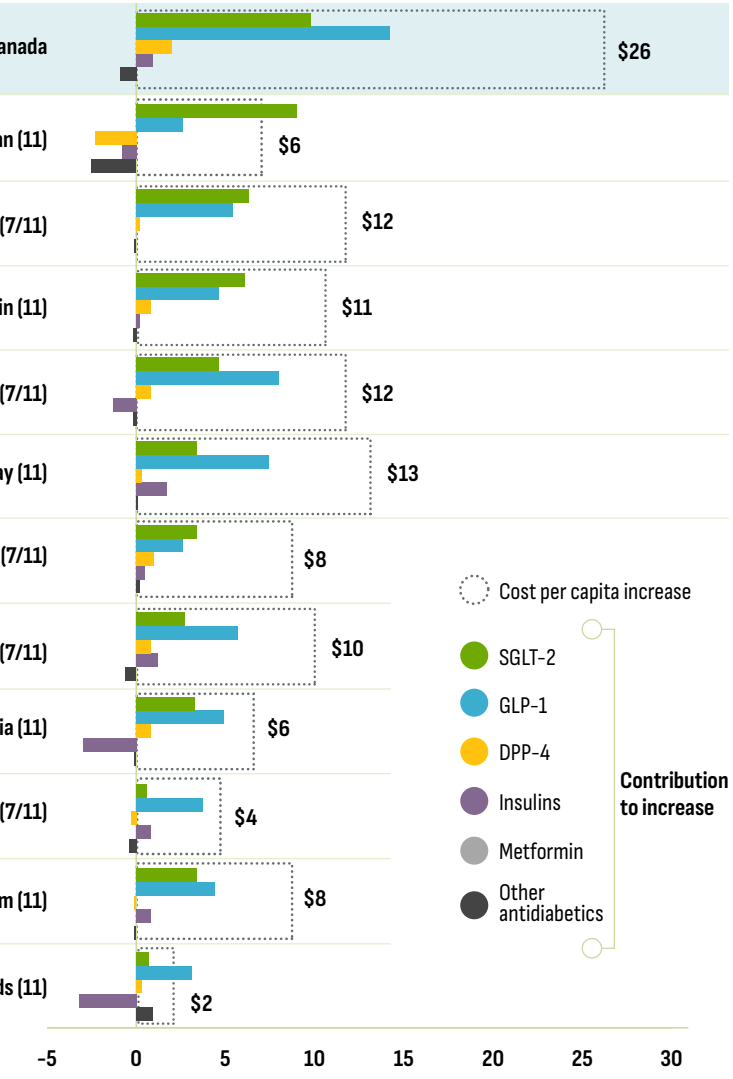
The shift to the new subclasses, particularly since the arrival of the SGLT-2's in the mid-2010's, is analysed in Figure 3.6. For example, Canada's cost per capita increased by $26 since 2017, from $46 (2017) to $71 (2021). Of this change, SGLT-2's and GLP-1's each contributed $9.8 and $14.2, respectively. This reflects the uptake of a new class (SGLT-2's) and the impact of semaglutide on the growth of the GLP-1 subclass. The modest $2.0 contribution by DPP-4's is consistent with an established class facing competition.

Insulins contributed $0.9, and all other antidiabetic drugs mitigated the increase with a cost per capita decrease of $0.9. Similar results are observed across the PMPRB11 and only the magnitude of the change varies. However, while in most countries insulins contributed to modest growth, some countries saw the reverse effect: Japan (-$0.8), Sweden (-$1.3), Australia (-$3.0), and the Netherlands (-$3.2).

Figure 3.6

Increase in cost per capita, contribution of each subclass, Canada and PMPRB11, 2017 to 2021 (CAD)

Change by subclass					
SGLT-2	GLP-1	DPP-4	Insulins	Other	
$9.8	$14.2	$2.0	$0.9	-$0.9	Canada
$9.0	$2.6	-$2.3	-$0.8	-$2.5	Japan (11)
$6.3	$5.4	$0.2	$0.0	-$0.1	Germany (7/11)
$6.1	$4.6	$0.8	$0.2	-$0.2	Spain (11)
$4.6	$8.0	$0.8	-$1.3	-$0.2	Sweden (7/11)
$3.4	$7.4	$0.3	$1.7	$0.1	Norway (11)
$3.4	$2.6	$1.0	$0.5	$0.2	United Kingdom (7/11)
$2.7	$5.7	$0.8	$1.2	-$0.6	Italy (7/11)
$3.3	$4.9	$0.8	-$3.0	-$0.1	Australia (11)
$0.6	$3.7	-$0.3	$0.8	-$0.4	France (7/11)
$3.4	$4.4	-$0.1	$0.8	-$0.1	Belgium (11)
$0.7	$3.1	$0.3	-$3.2	$0.9	Netherlands (11)



Data sources: Organisation for Economic Co-operation and Development; IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022).

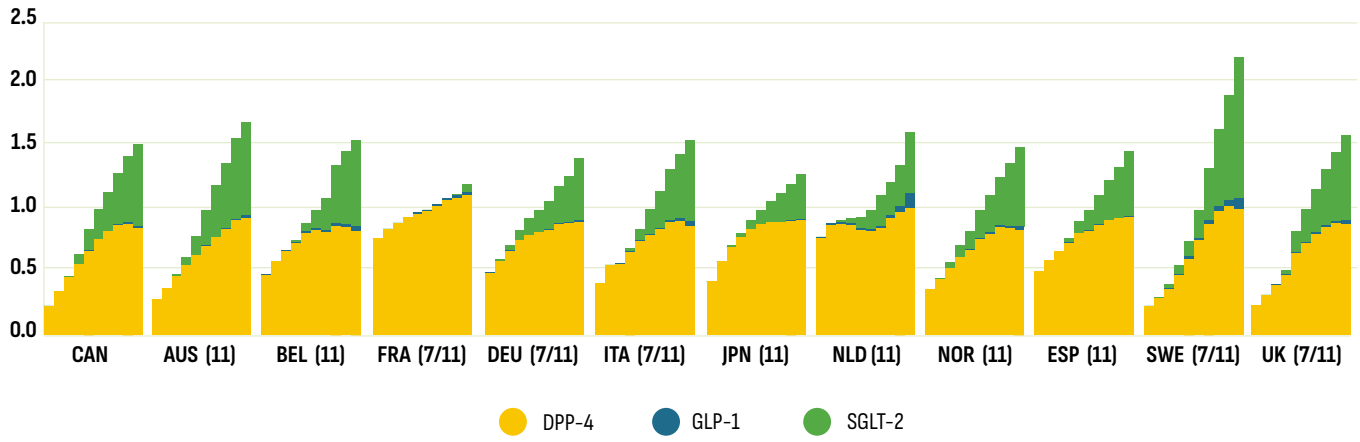
A closer look at shifts in utilization indicate that the changes in cost per capita discussed above were the result of increases in utilization of the relatively more expensive new-generation/non-insulin drugs and not the result of price increases. Figure 3.7 shows both overall growth and market share shifts in the units (Chart A) and costs (Chart B) for these subclasses over the past decade (2012-2021). The data are shown as a series of ten clustered stacked columns for each country. The data are indexed, with the total reported market for the drugs set at a value of 1 in 2017 across all countries (see Appendix A: Methodology Notes). It is important to keep in mind that both units and costs have limitations as metrics to analyse utilization. For example, units reported for semaglutide (Ozempic), the leading GLP-1, are comparatively low given its once per week dosing regimen, but costs remain substantial given its relatively higher price. This contrasts with DPP-4's and SGLT-2's that are taken once or twice a day. As such, GLP-1 utilization will be underestimated when measured in units and overestimated when measured in costs.

Overall, the international data suggest an evolving shift in prescribing from DPP-4's to SGLT-2's following the launch of SGLT-2's. However, it remains unclear whether the further decrease of DPP-4's is due to the launch of Ozempic or ongoing competition from the SGLT-2's. It is also unclear whether GLP-1 prescribing displaced SGLT-2's or if growth in GLP-1's was the result of off-label prescribing given semaglutide (Ozempic)'s documented effects on weight loss. It is worth noting that drugs in the SGLT-2 subclass are also indicated for the treatment of heart failure even in the absence of diabetes. It is not possible to determine if these drugs were used to treat diabetes or heart failure.

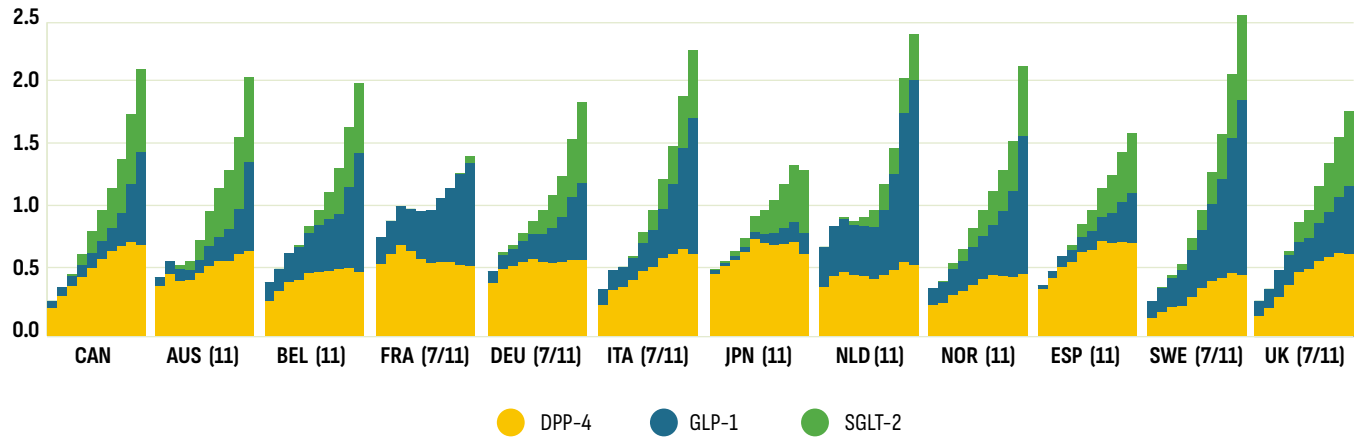
Figure 3.7

Indexed (2017) units and costs (CAD) by subclass (DPP-4, GLP-1, and SGLT-2), Canada and PMPRB11, 2012-2021

A: Units Index



B: Cost Index



Data source: IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022).

3.3 Canadian payers

This subsection looks at changes in antidiabetic drug spending by provincial (public) and private plans as well as out-of-pocket spending. The section begins with an overview of market share trends followed by an analysis of the three key cost drivers: utilization patterns, drug prices, and competition.

Who pays for drugs in Canada?

The administration and delivery of health care in Canada is a provincial responsibility subject to the provisions of the *Canada Health Act* (CHA).[8] Under the Act, provinces must provide access to doctor visits and hospital care without financial barriers but are not required to provide drug coverage outside the hospital setting. As a result, drug coverage varies across provinces, each with their own unique mix of public and private plans. Public plan coverage varies across provinces in terms of drugs covered (formulary listings), cost-sharing rules (co-pays, deductibles, and maximums), and populations covered. Finally, many Canadians incur out-of-pocket drug expenses (cash market) either because they have not met their plan's deductible, a drug is not covered, or they are not covered by a plan.

The two examples below illustrate the policy approaches that govern major drug programs administered by provinces‡.

Example 1: First payer, universal approach. British Columbia's Fair Pharmacare plan covers all residents regardless of age. Patient ability to pay is factored into the program with an income-based deductible (for example, the deductible is $2,000* for a family with a net income of $67,500†). Spending on eligible drugs (listed on the formulary) are applied toward this deductible regardless of payment source, whether paid through a private insurer or out-of-pocket.

Example 2: Population-defined, mixed approach. Program eligibility in the Ontario Drug Benefit program is defined according to set criteria. It is the first payer for seniors (≥65), social assistance recipients, and people aged 24 and younger without private coverage. Cost sharing is low and only seniors that do not meet the "low-income" threshold are required to meet a $100 deductible. Residents facing substantial drug costs may be eligible for the Trillium drug program if they meet an income-based deductible. While this deductible is similar in size to the one in British Columbia, it is administered as a "last payer" which means that only out-of-pocket expenses are applied to the deductible.

Notes:

* Deductible amount specified in the Fair PharmaCare assistance levels table (consulted January 2023).

† $67,500 is the "Median after-tax income, economic families and persons not in an economic family" for British Columbia in 2020 as reported by Statistics Canada.

‡ The examples provided are the largest programs; they are not an exhaustive list.

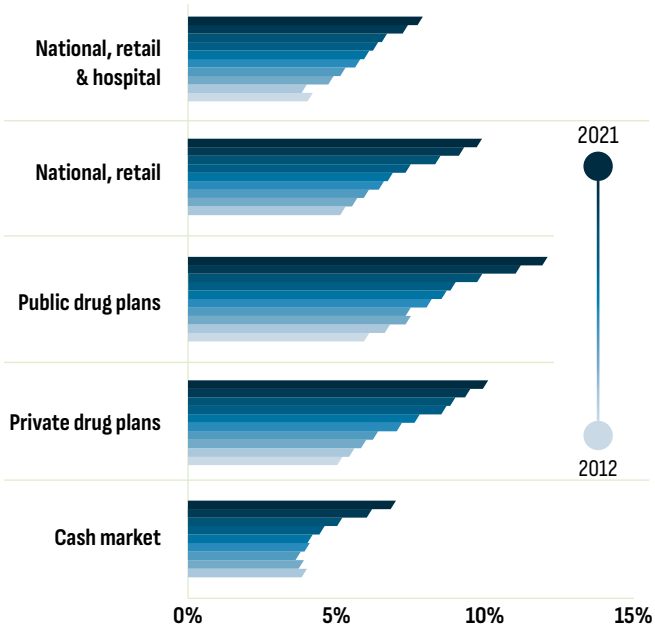
For all market segments and across all jurisdictions, growth in antidiabetic drug spending has outpaced the growth in the overall drug market, resulting in an increased share for antidiabetic drugs (see Figure 3.8).

Results across market segments and jurisdictions only vary in the size of this change over time. Nationally (Chart A), the overall retail market reached a 10% market share, and provincially (Chart B) some jurisdictions approached 15%.

Figure 3.8

Antidiabetic share of total drug market, 2012-2021

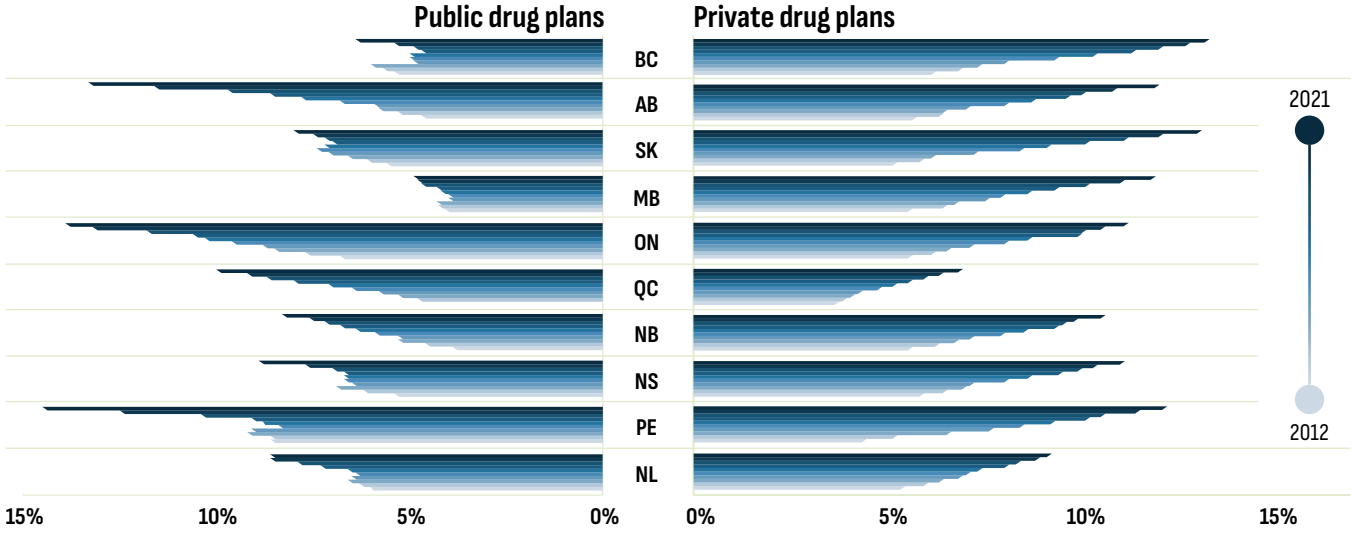
A: National averages



Data sources (data extracted in Q4-2022):

- National, retail and hospital: IQVIA MIDAS® Database, all rights reserved.
- National, retail: IQVIA Payer Insights Database
- Public drug plans: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information. National average does not include Quebec (see Methods section). Quebec shares in Chart B are estimated from IQVIA Payer Insights Database
- Private drug plans: IQVIA Private Pay Direct Drug Plan Database
- Cash market: IQVIA Payer Insights Database

B: Public and private drug plans by province



Data sources (data extracted in Q4-2022):

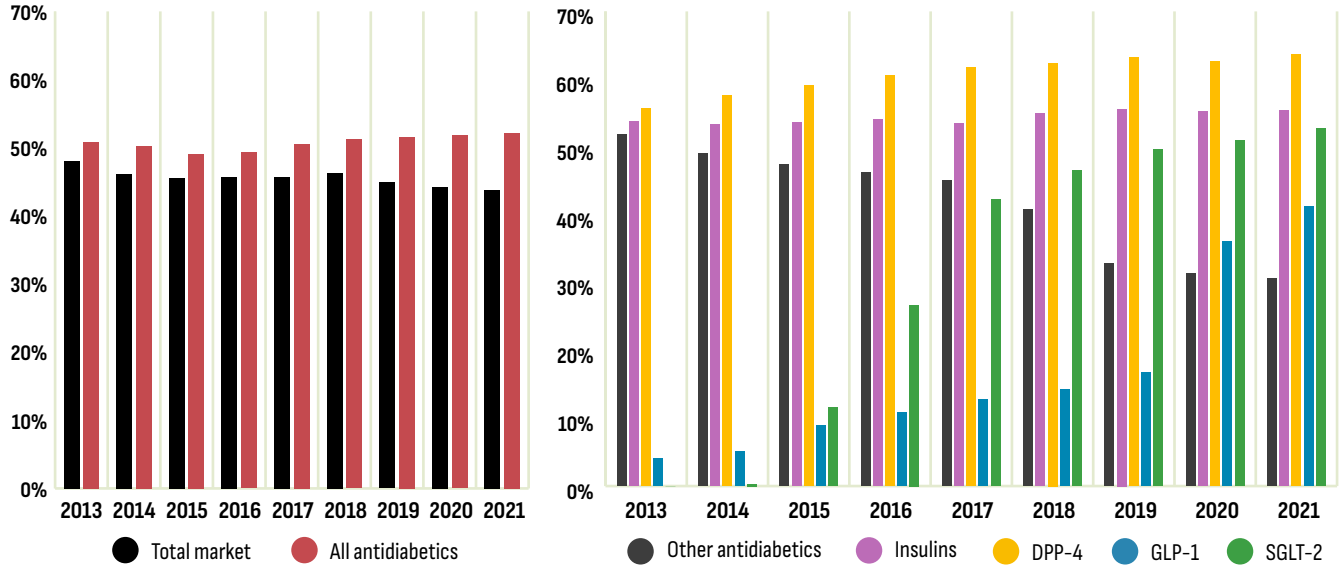
- Public drug plans, all provinces except Quebec: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
- Public drug plans, Quebec only: IQVIA Payer Insights Database
- Private drug plans: IQVIA Private Pay Direct Drug Plan Database

While spending on antidiabetic drugs has outpaced the growth in the overall drug market, public drug programs have continued to cover roughly half of the spending on this class every year. As shown in Figure 3.9 (Chart A), overall share of spending by public plans was 51% in 2013, falling to 49% in 2015 and 2016, and remained at 52% from 2019 to 2021.

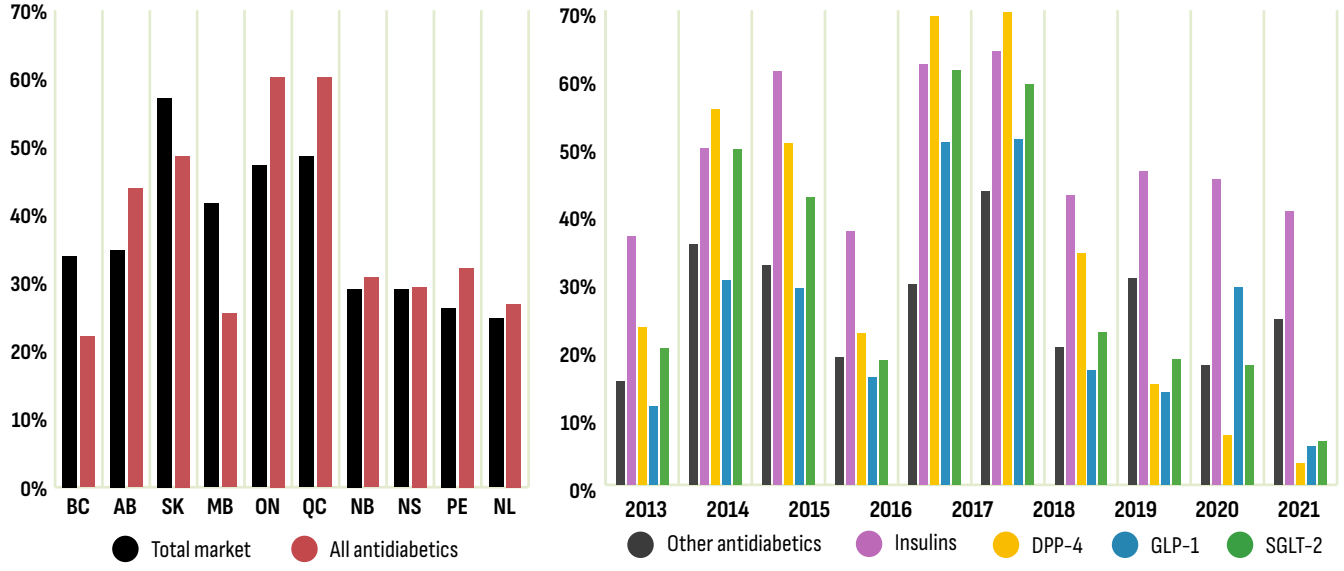
This occurred while public spending on all drugs declined steadily from 48% in 2013 to 44% in 2021. At the subclass level, the increase in the public share of GLP-1' and SGLT-2's reflects the evolution of formulary listing decisions. Finally, the public sector share of spending by province (Figure 3.9, Chart B) is reflective of provincial plan eligibility criteria and drug coverage (see text box: *Who pays for drugs in Canada?*).

Figure 3.9
Public sector share of spending

A: National, 2013–2021



B: By jurisdiction and subclass, 2021



Data source: IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022). All rights reserved.

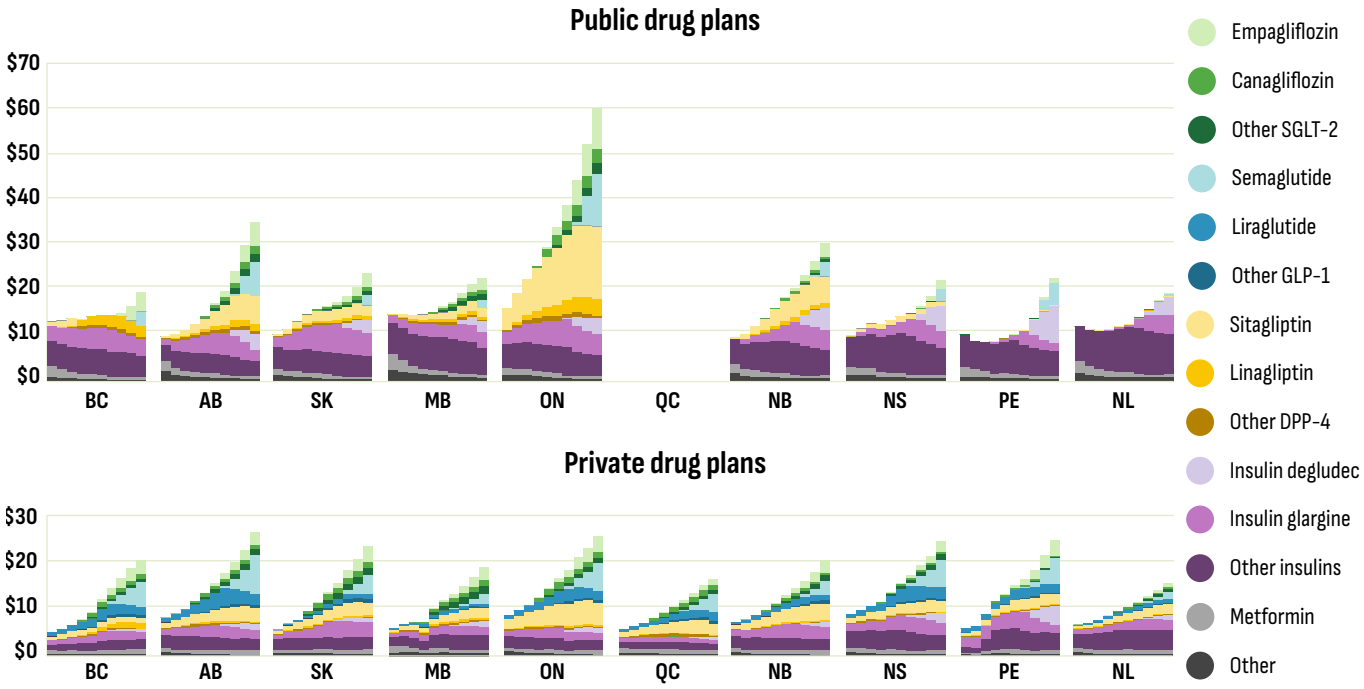
Figures 3.10 and 3.11 show utilization patterns at the provincial level for both public and private drug plans from 2012 to 2021. In both cases, standardization metrics were calculated to better compare trends and market shares across jurisdictions. Data in Figure 3.10 are standardized according to each plan's spending on metformin (first-line drug therapy for type 2 diabetes). In other words: "For every dollar spent on metformin in 2017, how much did the program spend on other drugs and how did this change over time?" Alternately, data in Figure 3.11 focus exclusively on utilization by analysing claims (paid prescriptions) rather than costs. The results are shown as a series of ten clustered stacked columns which have been indexed where total claims are set to one in 2017 (see Appendix A: Methodology Notes).

For each dollar spent on metformin in 2017, the new-generation/non-insulin drugs saw the greatest increases for both public and private drug plans (Figure 3.10).

The greatest increase was for Ontario's public drug plan, a result consistent with the plan's decision to list DPP-4's, GLP-1's, and SGLT-2's as open benefits rather than restricting access as is the case in all other provincial programs. For every dollar of metformin spent in 2017, Ontario spent $47 on new-generation/non-insulin drugs in 2021, nearly double Alberta's $25 spending and triple New Brunswick's $15 spending. Spending on GLP-1's was virtually non-existent in provincial plans for most of the period analysed until some provinces listed semaglutide (Ozempic). However, this subclass accounted for a larger market share in the private drug plans where access was generally less restricted. There has been considerable media attention concerning the extent to which semaglutide (Ozempic) is being prescribed off-label for weight loss. However, administrative databases do not include the reason for prescribing and this issue was not evaluated. Finally, insulin remained relatively stable, as a result of the market entry of degludec (Tresiba); biosimilar policies related to glargine (Lantus); and changes in formulary status for long-acting insulins. These are explored later in this subsection.

Figure 3.10

Drug plan spending for antidiabetic drugs standardized to $1 of metformin in 2017, 2012-2021



Notes:

- Quebec public drug plan data not shown here because it is not included in the NPDUIS database and estimates based on the IQVIA Payer Insights database were incompatible due to cost reporting differences.
- Sales for each molecule include sales for versions in combination with metformin. For example, sales of empagliflozin include both sales for empagliflozin alone (Jardiance) and empagliflozin and metformin (Synjardy).

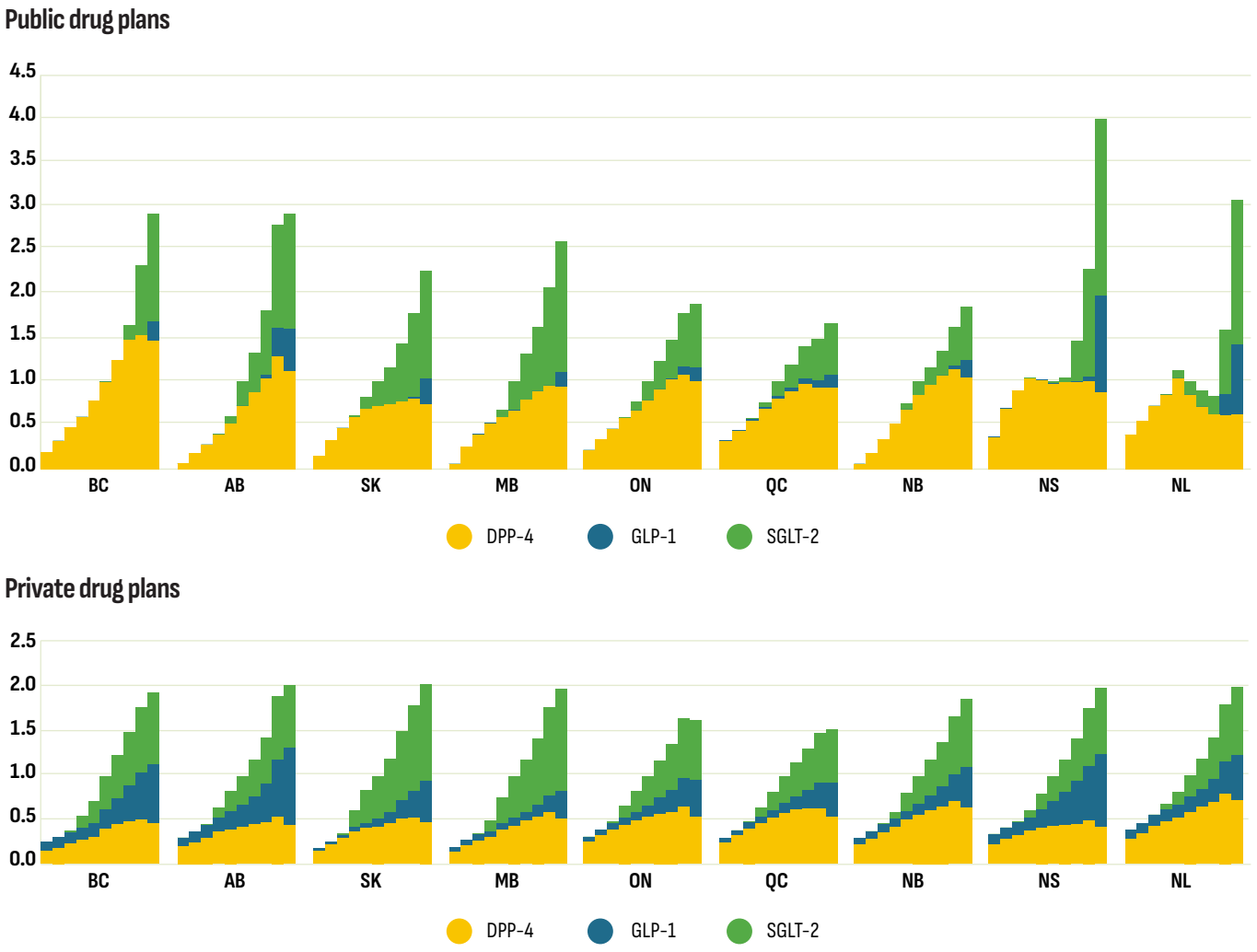
Data sources (data extracted in Q4-2022):

- Public drug plans: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information. All jurisdictions except Quebec.
- Private drug plans: IQVIA Private Pay Direct Drug Plan Database.

An analysis of claims (paid prescriptions) in Figure 3.11 reveals similar patterns and confirms that the growth in GLP-1's is not solely driven by the cost of these drugs. In the public sector, the entry of SGLT-2's coincides with a slowing rate of growth in DPP-4's well before the listing of semaglutide (Ozempic) but the latter likely contributed to further market erosion of the DPP-4 subclass. Finally, growth in SGLT-2's is likely driven by both patients with and without a diabetes diagnosis as these drugs are also indicated for heart failure.

Figure 3.11

Drug plan claims indexed to 2017, DPP-4, GLP-1, and SGLT-2 subclasses, 2012-2021



Note: Prince Edward Island not included due to program changes resulting in distorted indexed data.

Data sources (data extracted in Q4-2022):

- Public drug plans, all provinces except Quebec: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
- Public drug plans, Quebec only: IQVIA Payer Insights Database.
- Private drug plans: IQVIA Private Pay Direct Drug Plan Database.

As the prevalence of diabetes is expected to increase in coming years (see Section 1), payers can mitigate cost pressures by implementing formulary management strategies to balance optimal drug therapy for the patient while keeping health care budgets sustainable. Provincial plans can limit access to expensive drugs by requiring that other, less-expensive, therapies be attempted first.

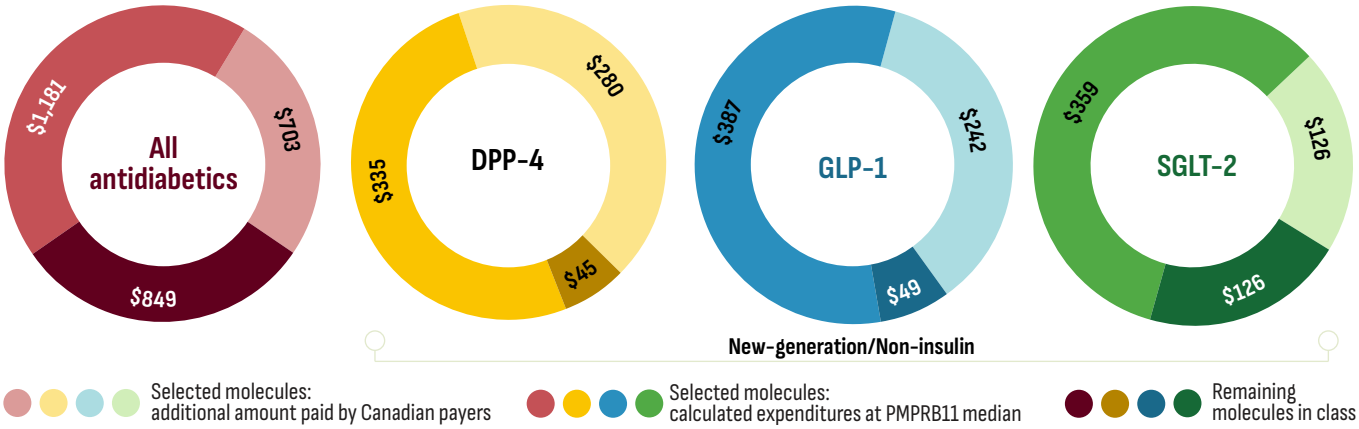
This is the case for most new-generation/non-insulin drugs that are listed with criteria in all provinces except Ontario, where they are open benefits. And while provinces can also encourage the use of less expensive generics, all drugs in the DPP-4, GLP-1, and SGLT-2 subclasses were not yet facing generic competition during the study period.

As discussed in subsection 3.1, Canadian prices for top-selling antidiabetic drugs were higher than the calculated PMPRB11 median price. As shown in Figure 3.12, the implication of this differential is $703M in savings nationally (retail and hospital) that could have been achieved based on calculated sales using the PMPRB11 median price ($1,181M) versus actual Canadian sales at list prices ($1,884M=$1,181M+$703M), while the remaining drugs not selected for price comparisons remain at $849M (see data for "all antidiabetics" in Figure 3.12).

Except for insulin degludec (Tresiba), all top-selling drugs selected for this analysis are new-generation/non-insulin drugs and their respective cost implications are also shown in Figure 3.12. The greatest contributor to the overall differential ($703M) was the DPP-4 subclass ($280M), accounting for 40% of the differential. This was followed by the GLP-1 subclass ($242M) and the SGLT-2 subclass ($126), which accounted for 34% and 18% of the differential, respectively. Insulin degludec (not shown) accounted for 8% ($56M). It is worth noting that payers may have already obtained some savings through confidential prices and and rebates which are not included in the available data.

Figure 3.12

Cost implications for all antidiabetic drugs and by subclass, national retail, and hospital markets (millions, CAD), 2021



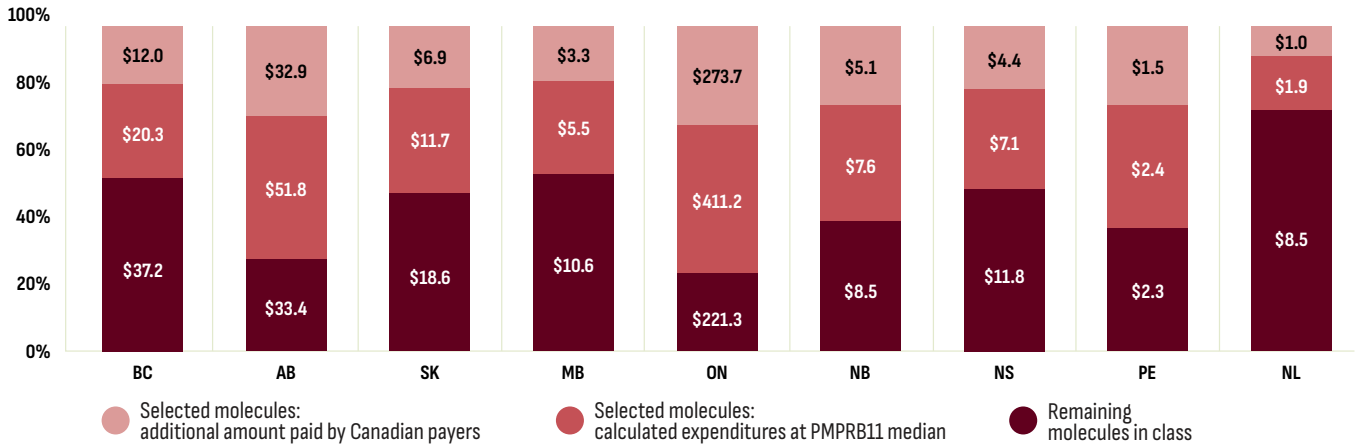
Data source: IQVIA MIDAS® Database, prescription retail and hospital markets (data extracted in Q4-2022). All rights reserved.

The cost implications for the top-selling antidiabetic drugs were also calculated for each province (see Figure 3.13). This cost differential was highest in Ontario and Alberta both in terms of absolute spending ($273.7M and $32.9M, respectively) and as a proportion of overall spending on antidiabetic drugs (30% and 28%, respectively).

This cost differential represented 4% of both provinces' total overall drug plan spending (all drugs, not shown). The cost implications for the other provinces (except Newfoundland) hovered near 20% of spending on antidiabetic drugs, representing a 1% to 3% share of overall drug plan spending.

Figure 3.13

Cost implications for all antidiabetic drugs, public plans, by jurisdiction (millions, CAD), 2021



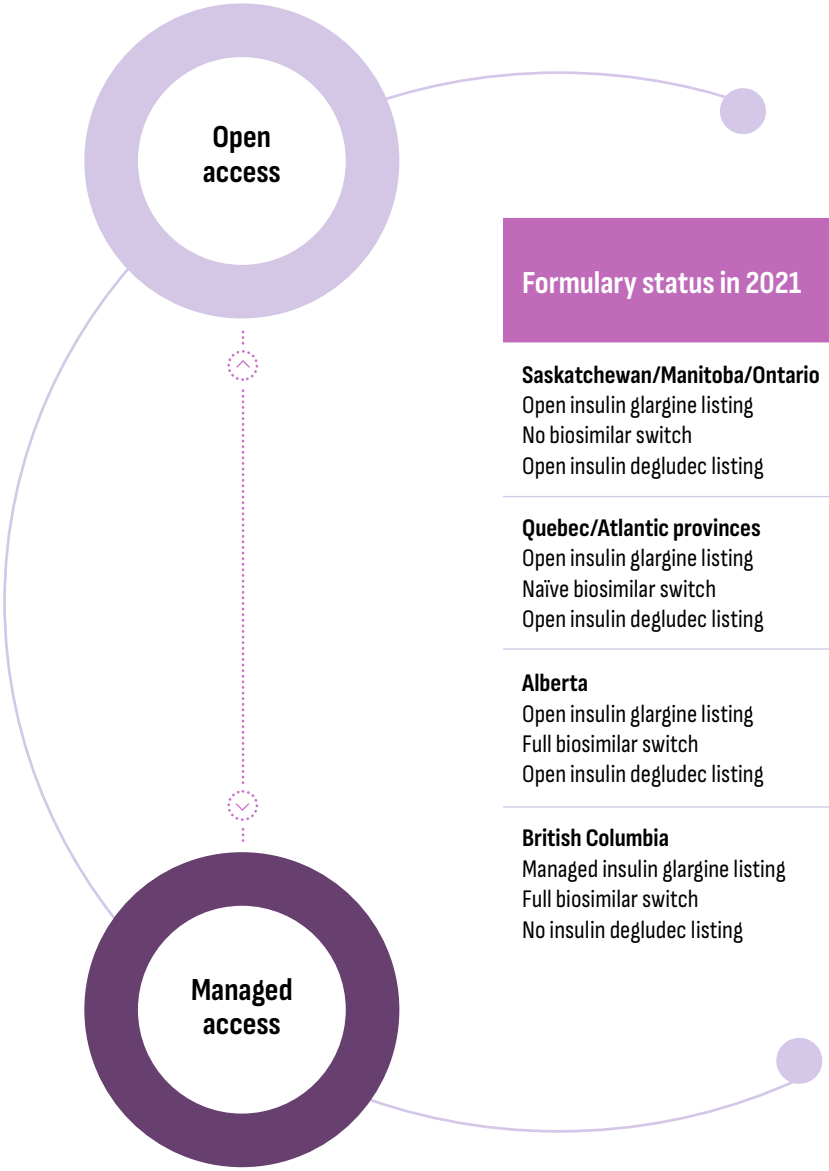
Data source: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information (data extracted in Q4-2022).

While generic competitors for new-generation/non-insulin drugs had yet to enter the market, provincial drug plans began implementing policies to encourage a switch to biosimilars in the insulin market. The remainder of this subsection presents a case study examining the impact of biosimilar switching policies for insulin glargine on utilization patterns by province. The analysis also looks at the impact of concurrent formulary changes as well as the launch of insulin degludec (Tresiba) on total insulin glargine utilization during that time.

Figure 3.14 summarizes the key formulary changes related to both insulin glargine and insulin degludec beginning in 2017/18 and up to 2021.[v] The early biosimilar switching policies, beginning in 2017, required naïve (new) patients to initiate treatment with the biosimilar version of insulin glargine, while patients already established on insulin therapy could continue to receive coverage for the brand (Lantus). By the end of 2021, only British Columbia, Alberta, and New Brunswick mandated biosimilar switching. However, New Brunswick's policy was implemented very late in 2021 and its impact will only become apparent in the 2022 data. Consequently, in this analysis, New Brunswick is categorized as a province with a naïve biosimilar policy in effect upon listing biosimilars in late 2017.

Figure 3.14

Public drug plan policy history, insulin glargine and insulin degludec



Formulary status in 2021	Biosimilar policy history
Saskatchewan/Manitoba/Ontario Open insulin glargine listing No biosimilar switch Open insulin degludec listing	Status for insulin glargine in Ontario and Saskatchewan remained open benefit throughout the study period. Access to insulin glargine in Manitoba was managed until October 2018 after which it became open benefit.
Quebec/Atlantic provinces Open insulin glargine listing Naïve biosimilar switch Open insulin degludec listing	Upon biosimilar listing, insulin glargine status changed from limited to full benefit for the biosimilar only. Only previously established patients have access to Lantus.
Alberta Open insulin glargine listing Full biosimilar switch Open insulin degludec listing	Alberta has maintained open access to insulin glargine throughout the period; however, as of January 2021, only the biosimilar is open benefit and Lantus is effectively de-listed.
British Columbia Managed insulin glargine listing Full biosimilar switch No insulin degludec listing	Insulin glargine listing status has remained limited throughout the study period. By the end of 2019, Lantus was de-listed and only the biosimilar remains listed under special authorization.

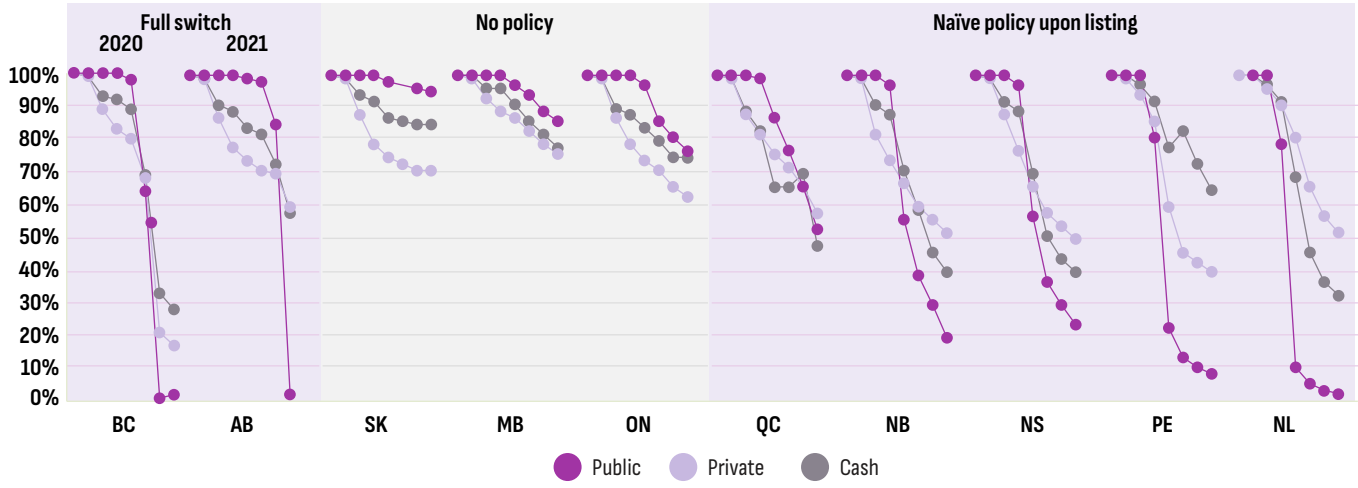
v Full Biosimilar policies announced after 2021: Saskatchewan (2023), Ontario (2023), Quebec (2022), Nova Scotia (2023). As of January 2023, Manitoba has not announced a policy.

The effect of a full biosimilar switching policy in the British Columbia and Alberta public drug plans was swift and complete while provinces with naïve biosimilar policies (Quebec and Atlantic provinces) saw a slower pace of change. As shown in Figure 3.15, Lantus' share of insulin glargine claims in British Columbia and Alberta remained near 100% up until the policy was fully implemented and fell to virtually 0% after implementation (by 2020 in British Columbia and by 2021 in Alberta). In contrast, Lantus' market share remained well above 75% by 2021 in provinces without any biosimilar policy (Saskatchewan: 95%; Manitoba: 86%; and Ontario: 77%). The naïve biosimilar policies in Quebec and in Atlantic provinces (implemented in 2017/18) gradually shifted prescribing toward biosimilars resulting in market shares for Lantus below 25% by 2021. Private drug plans in British Columbia, which are often more integrated with the public plan[7], matched the dramatic change observed in the public sector. The cash market saw a similar change since only drugs covered by the provincial plan are applied to the income-based deductible in British Columbia. By contrast, populations covered by private and public plans in Alberta are very distinct, resulting in little spillover between the two market segments. Despite a near complete biosimilar switch in the public sector, Lantus' market share only dropped by 10 percentage points after the biosimilar policy in both private and cash markets (from roughly 70% to 60%).

Moreover, uptake of biosimilars in both the private and cash markets in the absence of a biosimilar switching policy was consistently greater than in public plans. (The absence of a policy can be observed both prior to implementation and in provinces without a policy.) The reason may be that patients in the private and cash markets are on average younger and initiating treatment compared to patients in public plans that might be older and long-established on therapy. Even in a province like British Columbia where the universal program does not distinguish between seniors and non-seniors, younger patients may not reach their yearly deductible as they may have lower overall drug expenses due to fewer co-morbidities or beginning therapy mid-year. Another consideration in the cash market is drug affordability for patients who pay out-of-pocket. In these cases, biosimilars provide cost savings of 22%, or $265 per year for an average patient.[vi] This reasoning also holds in provinces with naïve patient switching policies (Quebec and Atlantic provinces) where Lantus' loss of market share in private and cash markets was greater than in the provinces where no biosimilar policy was in effect. It appears that the biosimilar policy targeting naïve patients changed prescribing habits in all market segments.

Figure 3.15

Lantus share of insulin glargine claims, 2014 to 2021



Data sources (data extracted in Q4-2022):

- Public drug plans, all provinces except Quebec: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
- Public drug plans, Quebec only: IQVIA Payer Insights Database.
- Private drug plans: IQVIA Private Pay Direct Drug Plan Database.
- Cash: IQVIA Payer Insights Database.

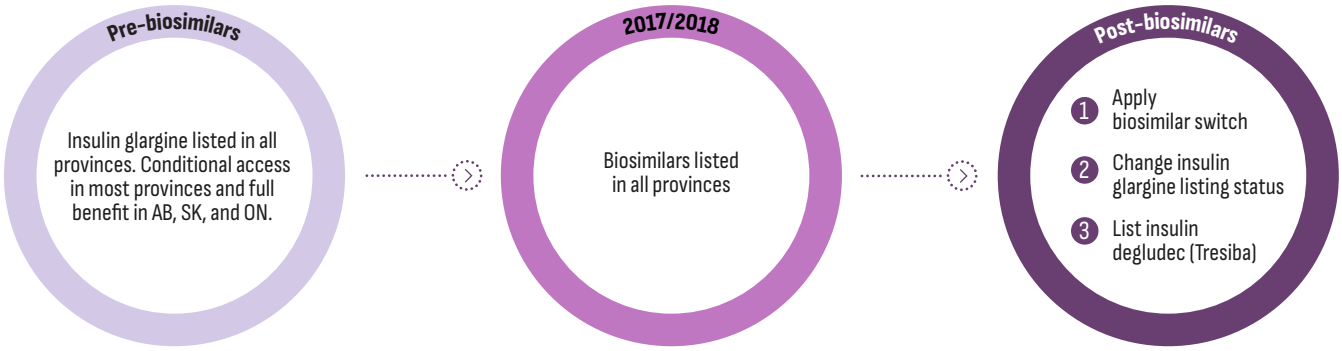
vi Based on the Ontario Drug Benefit program prices for the 100U/mL Cartridge, 5x3mL package, published in the online formulary (assumes an 8% mark-up and does not include dispensing fee). Dosage from Defined Daily Dose for insulin glargine published online by the World Health Organization website. (Both websites accessed January 2023.)

In addition to the formulary listing decisions affecting insulin glargine claims, all provinces except British Columbia listed insulin degludec (Tresiba), a new long-acting insulin, as an open benefit (see Figures 3.14 and 3.16).

The intersection of these evolving decisions resulted in a complex web of market effects which are the focus of the remainder of this subsection.

Figure 3.16

Insulin glargine market timeline and factors affecting insulin glargine claims



The trends discussed below are illustrated in Figure 3.17. They are presented as an index for greater clarity and comparisons across jurisdictions. Newfoundland and Prince Edward Island are not shown due to the small amount of data (see Appendix A: Methodology Notes).

- **British Columbia** is the only province where claims for insulin glargine remained relatively constant from 2017 to 2021 in the public plan. It is also the only plan that implemented a full biosimilar switching policy while simultaneously maintaining special authorization access for insulin glargine and not listing insulin degludec.

- By contrast, both **Saskatchewan and Ontario** maintained consistently open access to all insulin products including listing insulin degludec, and both experienced a gradual decline in insulin glargine claims by 2021 of 14% (index: 0.86) and 12% (index: 0.88), respectively.

- **Manitoba**'s near-50% increase in insulin glargine claims reflects its decision in 2018 to remove its restrictions on these insulins including listing insulin degludec.

- Before implementing its switching policy in 2021, **Alberta**'s approach and market dynamics were similar to those observed in Saskatchewan and Ontario, both provinces with open access for insulin glargine and insulin degludec. However, while the effect of its full biosimilar switch policy was essentially the same as British Columbia's, Alberta experienced the largest decline in overall insulin glargine claims (33%) of all jurisdictions. It is possible that the timing of its biosimilar policy, concurrent with listing insulin degludec, precipitated this decline and eroded cost savings generated by the biosimilar policy.

- Upon listing biosimilars in 2017/18, **Quebec and Atlantic provinces** removed reimbursement criteria for insulin glargine. The result in the Atlantic provinces is a substantial increase in insulin glargine claims. Quebec, however, did not experience a comparable increase, which may simply be due to the timing of policy changes which might have been more apparent between 2016 and 2017 and consequently are not apparent after 2017. Overall, Quebec and Atlantic provinces saw a more modest decline in insulin glargine claims despite listing insulin degludec, suggesting that the early naïve biosimilar policy provided sufficient time to adjust prescribing habits.

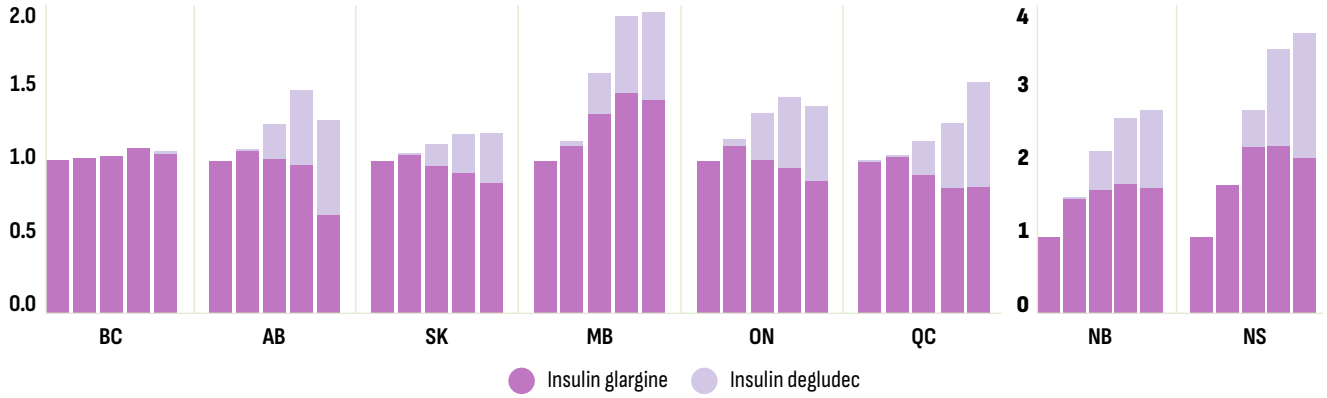
- As explained earlier, trends observed in **private plans** reflect the extent to which the public and private sectors are integrated. For example, in British Columbia, claims for insulin glargine remained relatively flat in both public and private drug plans and uptake of insulin degludec in private plans was lower than in any other province. Private plan trends in Alberta private plans do not mirror the public plan data. Rather, they look more like those observed in Ontario's private plans which are similarly distinct from their public counterparts.

- The **cash market** saw little uptake of insulin degludec compared to private plans. The cost of this drug may have been a contributing factor as patients paying out-of-pocket would pay an additional $506 per year (50% more) compared to the biosimilar for insulin glargine.[vii]

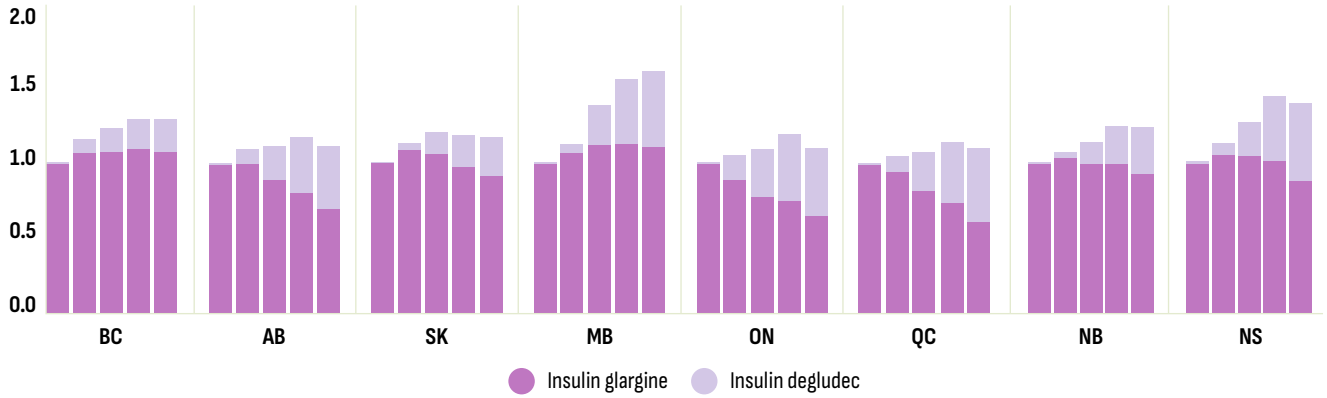
vii Based on the Ontario Drug Benefit program prices for insulin glargine (cartridge) and insulin degludec (Sol-Flextouch Pen), 100U/mL Cartridge, 5x3mL package, published in the online formulary (assumes an 8% mark-up and does not include dispensing fee). Dosage from Defined Daily Dose for insulin glargine published online by the World Health Organization website. (Both websites accessed January 2023.)

Figure 3.17
Indexed claims for insulin glargine and insulin degludec (2017-2021)

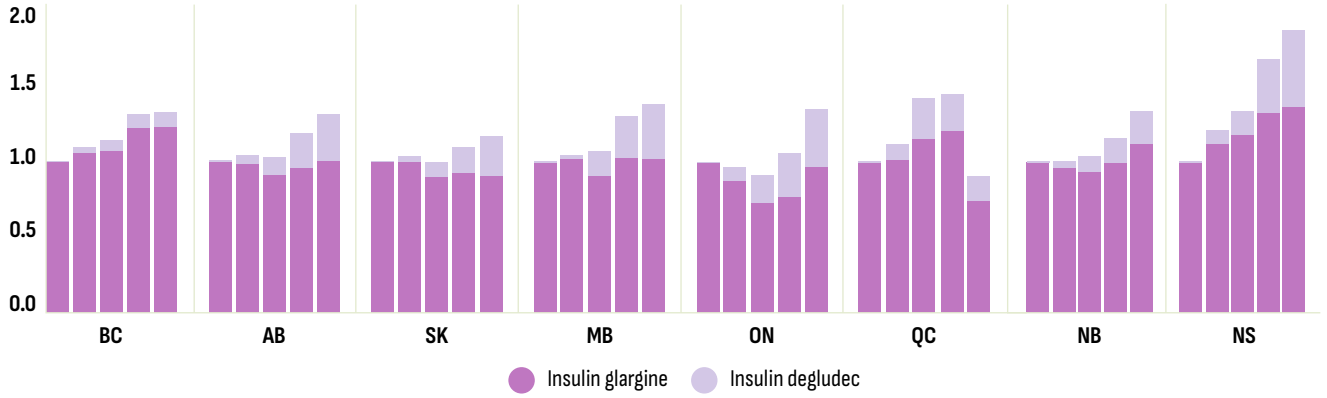
A. Public drug plans



B. Private drug plans



C. Cash



Data sources (data extracted in Q4-2022):

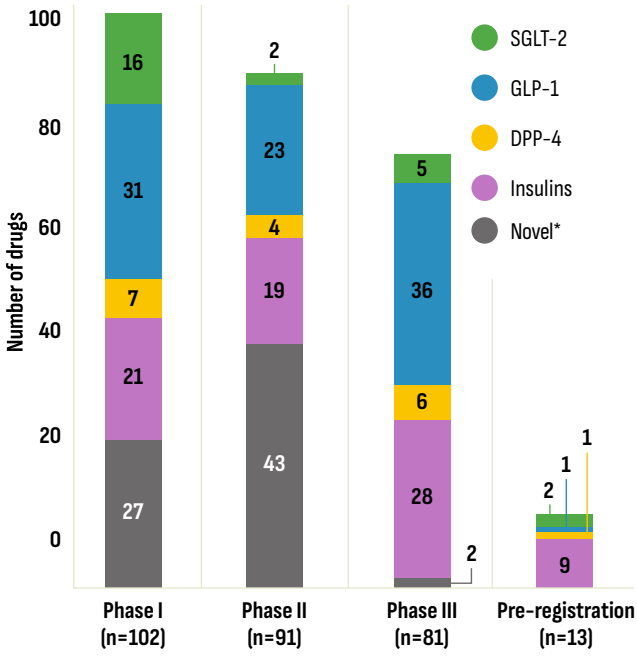
- Public drug plans: National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information. All jurisdictions except Quebec. Data for Quebec estimated from IQVIA Payer Insights Database.
- Private drug plans: IQVIA Private Pay Direct Drug Plan Database.
- Cash: IQVIA Payer Insights Database.

4 A Look into the Future

Since the launch of canagliflozin (Invokana) in 2014, no novel antidiabetic drug class has been approved (see Section 2). This may change in 2023, following Health Canada's approval of tirzepatide (Mounjaro) in November 2022, just months after approval by the US Food and Drug Administration (FDA) in May 2022. It is a first-in-class dual agonist compound indicated for type 2 diabetes affecting the activation of both GLP-1 and GIP (glucose-dependent insulinotropic polypeptide). This emerging generation of drugs, known as "twincretins" may offer additional benefits compared to GLP-1's alone, including improved blood sugar control and weight loss, as well as evidence of favourable cardiovascular impact.[9]

Looking further into the drug pipeline, there are 206 non-insulin and 77 insulin drugs at various phases of clinical development. As shown in Figure 4.1, there are ongoing clinical trials for drugs in all existing classes featured in this report (DPP-4, GLP-1, SGLT-2, insulins) as well as non-insulin drugs in a variety of novel drug classes. These include targets for glucokinase, adenosine monophosphate activated protein kinase, fibroblast growth factor receptor 1 and bile acid receptors.

Figure 4.1
Number of antidiabetic drugs in development by class and phase



Data Source: GlobalData Healthcare database (accessed January 2023).

* Novel drug classes; excludes insulins.

Over 80% of the drugs in the pipeline can be classified as "me-too"[viii] drugs, including all the drugs in Phase III and pre-registration, except for two drugs in clinical trials underway in China targeting various gene receptors. Drugs at this stage of development are still 2 to 5 years away from market, provided they remain clinically and commercially viable. Notably, two insulin products may have an impact on diabetes management due to their distinct formulations and dosing regimens. The first is a novel insulin receptor agonist in oral form (ORMD-0801) that is currently undergoing phase II and III clinical trials and has the potential to significantly impact therapy administration as an alternative to insulin injections. The second, insulin icodec, is a long-acting basal insulin analogue undergoing phase III clinical trials. Unlike currently available insulins that require daily injections, insulin icodec is only administered once weekly. This significant reduction in injection frequency may have an important impact on the management of diabetes for some patients.

It remains to be seen if, and to what extent, these novel classes of antidiabetic drugs and future "first-in-class" drugs will result in substantial treatment breakthroughs, if their benefits will be limited to niche populations, or if they will be one among many treatment options. Nevertheless, and perhaps more importantly, innovation in antidiabetic drugs reflects the evolving understanding of the complex mechanisms affecting human metabolism, shifting the focus beyond insulin. Not only have new-generation/non-insulin drugs changed prescribing for diabetic patients, but they are also the first antidiabetic drugs to be approved for indications outside of diabetes treatment, potentially with significant clinical and budgetary implications. These include indications for heart failure and kidney disease (SGLT-2's) and indications for weight management (GLP-1's) (see Section 2). And while the most recent addition, tirzepatide, is currently only indicated for type 2 diabetes, similar indications beyond diabetes may be on the horizon for this drug and a sign of things to come from the pipeline.

viii Me-too drugs are compounds that are novel yet structurally related to a first-in-class compound and have similar outcomes.

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Appendix A: Methodology Notes

Topic	Figures	Methodology
Cost per capita	Figure 3.3 Figure 3.4 Figure 3.5 Figure 3.6	Cost of antidiabetics drugs (or subclass) divided by the total population (census). It is a useful metric to compare spending in countries of varying sizes.
Index	Figure 3.7 Figure 3.11 Figure 3.17	An index is a useful way of displaying market trends when comparing markets of different sizes. In this report, the index year is 2017 which means that yearly totals, whether units or costs, are divided by the total for 2017 and resulting in a value of 1 for that year. For example, in Figure 3.7 (Chart A), total units sold in Canada were 559 million and 368 million in 2021 and 207, respectively. The index for 2021 was thus 1.521 (559 ÷ 368). The yearly indices were calculated for a group of subclasses or drugs. Each year's index was then divided according to the market shares for these subclasses or drugs in that year. For example, in Figure 3.7 (Chart A), the 2021 market share for each subclass in Canada was as follows: DPP-4 (56%); GLP-1 (1%); SGLT-2 (43%). These percentages were applied to the index of 1.521 (see above) resulting in a stacked column containing the following values: DPP-4 (0.852); GLP-1 (0.017); SGLT-2 (0.652). This approach of calculating an overall index which is then subsequently allocated according to market share avoids data distortions in percent growth rates that inevitably occur in the first few years post-launch. However, some distortions may occur in smaller markets or when external administrative factors (program changes) result in large changes.
$1 of metformin	Figure 3.10	Figure 3.10 answers the question: how much a payer spent on a subclass for every dollar spent on metformin in 2017. Metformin was selected as a reference for this calculation to provide an intuitive way to compare results that illustrate both market growth and evolving market shares. Some distortions may occur in smaller markets or when external administrative factors (program changes) result in large changes. This calculation follows the steps outlined below and based on the Ontario Drug Benefit (ODB) program data. ● First, spending on metformin is indexed. For example, spending on metformin was $14,867M and $8,551M in 2017 and 2021, respectively, which results in an indexed value of 0.575 ($8,551M ÷ $14,867) in 2021. ● Second, total antidiabetic spending is standardized for each payer according to the market share of metformin. In 2021 this share was 0.94% in the ODB and the indexed value for metformin spending was calculated above at 0.575. This index is then divided by the metformin share resulting in a standardized amount of $61.0 (0.575 ÷ 0.94% = $61.0). ● Third, the standardized total ($61.0) is then allocated to the subclasses and drugs according to their respective market shares for that year. For example, sitagliptin's 2021 adjusted amount, $16.2, is calculated by applying its 2021 market share, 26.6%, to the adjusted total spending (26.6% x $61.0 = $16.2).

Appendix B: Assessments, Recommendations, Negotiation Status, and Reimbursement Decisions

Medicinal ingredient (trade name) and manufacturer	PMPRB HDAP assessment	CADTH recommendation	pCPA negotiation status	Public reimbursement
DPP-4				
Sitagliptin (Januvia) Merck Canada Inc.	Category 3 (slight or no improvement)	LWCC	Completed	All provinces except BC, YT and NIHB
Sitagliptin/metformin (Janumet) Merck Canada Inc.	Category 3 (slight or no improvement)	LWCC	Completed	All provinces except BC, YT and NIHB
Saxagliptin (Onglyza) Bristol-Myers Squibb Canada Co.	Category 3 (slight or no improvement)	LWCC	Completed	All provinces, YT and NIHB
Saxagliptin/metformin (Komboglyze) Bristol-Myers Squibb Canada Co.	S/N	LWCC	Individual by province/ territory	All provinces, YT and NIHB
Linagliptin (Trajenta) Boehringer Ingelheim (Canada) Ltd.	S/N	LWCC	Completed in combination with Jentadueto	All provinces, YT and NIHB
Linagliptin/metformin (Jentadueto) Boehringer Ingelheim (Canada) Ltd.	S/N	LWCC	Completed in combination with Trajenta*	All provinces, YT and NIHB
Alogliptin (Nesina) Takeda Canada Inc.	S/N	DNL	Decision not to negotiate	Not listed
Alogliptin/metformin (Kazano) Takeda Canada Inc.	S/N	DNL	Decision not to negotiate	Not listed
SGLT-2				
Canagliflozin (Invokana) Janssen Inc.	S/N	LWCC	Completed	All provinces except BC, YT and NIHB
Canagliflozin/metformin (Invokamet) Janssen Inc.	S/N	LWCC	Closed as agreements were not reached	Not listed
Empagliflozin (Jardiance) Boehringer Ingelheim (Canada) Ltd.	S/N	LWCC	Completed**	All provinces except BC, YT and NIHB
Empagliflozin/metformin (Synjardy) Boehringer Ingelheim (Canada) Ltd.	S/N	LWCC	N/A	Not listed
Dapafliflozin (Forxiga) AstraZeneca Canada Inc.	S/N	LWCC***	Completed	All provinces except BC, YT and NIHB
Dapafliflozin/metformin (XigDuo) AstraZeneca Canada Inc.	S/N	LWCC	Completed	All provinces except BC, YT and NIHB

Combination of DPP-4 and SGLT-2 approved and cancelled post market in Canada				
Empagliflozin/linagliptin (Glyxambi) *** Boehringer Ingelheim (Canada) Ltd.	S/N	No CDR report available	Not listed	N/A
Empagliflozin (Steglatro) Merck Canada Inc	S/N	DNL	Concluded without agreement	Not listed
Combination of DPP-4 and SGLT-2 approved and not marketed in Canada				
Dapagliflozin/saxagliptin (Qtern) Boehringer Ingelheim (Canada) Ltd.	N/A	N/A	N/A	N/A
GLP-1				
Liraglutide (Victoza)	S/N	DNL	Concluded without agreement	Not listed, restricted in QC
Exenatide (Byetta)	S/N	DNL	Concluded without agreement	Not listed
Exenatide (Bydureon)	S/N	Not available	N/A	Not listed
Dulaglutide (Trulicity)	S/N	LWCC	Concluded without agreement	Not listed, restricted in QC
Lixisenatide (Adlyxine)	S/N	LWCC	Completed	Listed only in ON and NIHB,NU, NT restricted in AB, SK, NB
Semaglutide (Ozempic)	S/N	LWCC	Completed	Listed in ON, NIHB, YT and restricted in all other provinces
Semaglutide (Rybelsus)	Not yet reviewed	LWCC	Active negotiation	Not listed
Insulins				
Insulin degludec (Tresiba)	Not reviewed	LWCC	Completed	All provinces, except BC
Insulin degludec/liraglutide (Xultophy)	Not reviewed	LWCC	Concluded without agreement	Not listed
Insulin glargine/lixisenatide (Soliqua)	Not reviewed	LWCC	Completed	Listed only in ON and NIHB, restricted in SK

Source: Formulary listings for Public Coverage of Diabetes Medications in Canada: https://www.diabetes.ca/DiabetesCanadaWebsite/media/Advocacy-and-Policy/Provincial%20and%20Territorial%20Formulary%20Chart/PT-formulary-listings_July-2021.pdf

S/N: slight or no improvement; LWCC: list with criteria or conditions; DNL: do not list.

A Category 3 drug product is a new DIN of a non-comparable dosage form of an existing medicine or the first DIN of a new chemical entity. These DINs provide moderate, little or no therapeutic advantage over comparable medicines.

* This followed an earlier decision to negotiate individually by P/F/T

** Negative recommendation for the more recent submission to be used in combination with metformin and a sulfonylurea

*** Sold in Canada, small sales for privately insured and cash paying individuals

Data sources: PMPRB, CADTH, pCPA, CIHI.