EXPRESS SCRIPTS CANADA

PRESCRIPTION DRUG TREND REPORT

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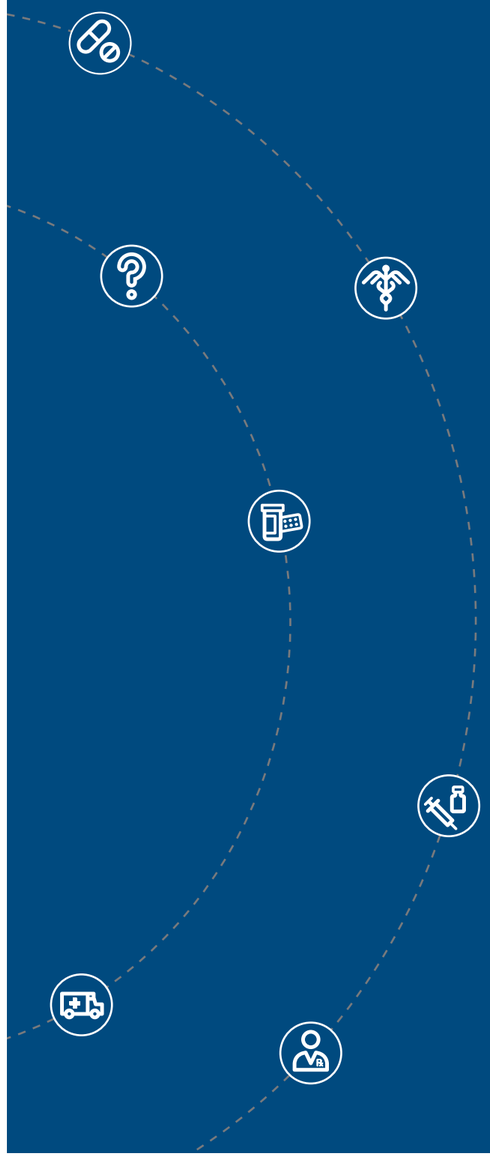

EXECUTIVE

SUMMARY

EXECUTIVE SUMMARY

This year's Prescription Drug Trend Report maps a continued deceleration in the longer-term trend of rapid increases in private plan spending. When we began reporting on the pharmaceutical landscape two decades ago, the era of blockbuster drugs was still in its infancy, about to present the first major challenges to sustainable prescription drug coverage. In 1998, prescription drug spending in Canada (not including hospital-administered drugs) was $8 billion*. In 2018, that prescription drug spending was expected to reach $33.7 billion**, the culmination of a trend that far outpaced broader inflation.

In the past few years, however, benefit plan design that empowers plan members, along with patent expirations and policy leadership on drug prices, have contributed to a welcome reprieve, with overall increases in cost per claimant of 2.9%, 2.5% and 0.9% in 2016, 2017 and 2018, respectively.

At the same time, the end of the blockbuster drug era has shifted pharma innovation efforts, and the drug development pipeline is now focused on million-dollar-per-treatment drugs and emerging gene therapies. Even as spending on traditional medicines has at least temporarily stabilized, these high-cost, specialty drugs are driving specialty spending higher in recent years, with a positive trend of 6.9% in 2018. Almost triple Canada's overall inflation in these periods, these increases make it clear that specialty medicines must be carefully and proactively managed. The stratospheric prices of these breakthrough treatments mean that benefit plan design must be equally innovative to protect treatment access and plan sustainability.

By applying our clinical expertise to the analysis of the "big data" inherent in processing claims for millions of Canadians, Express Scripts Canada has identified the claim patterns that reveal where plan members need support and where spending that doesn't contribute to better health can be avoided. For the first time, we've also investigated the variations of needs between members of different life stages. Within the report, you'll find examples of generational challenges and targeted solutions through the lens of a single but typical Canadian family.

In 2018, also for the first time, we've added adherence patterns to our therapy class reporting. It has become increasingly evident that nonadherence, the inability of patients to take their medications as prescribed, is a primary cause of poorer health outcomes and higher spending. The result of this research is an even more nuanced understanding of the importance of customized tools to meet the unique needs of plan members at different stages of their life and health.

DRUG TRENDS AT A GLANCE

- Implemented in Ontario on January 1, OHIP+ was a major factor in 2018. As a result, claims dropped for those under age 25 by 63% compared to 2017, and spending in this demographic fell by 52% with a significant impact on overall drug spending. (Without OHIP+, the increase in overall spending trend in 2018 would have been closer to 2.8%.) In 2019, we will see the reversal of this impact, as the province's new government has redesigned OHIP+ to remove coverage eligibility for those with access to private drug plans, effective April 1.
- Specialty spending has surged from 15% of total spending in 2008 to 30% in 2016, to 33% in 2018.
- Patients with chronic conditions had especially high levels of nonadherence, including 70% of plan members with asthma, 47% with cancer, 45% with diabetes and 45% with inflammatory conditions. Treatment complexity is associated with poorer adherence: with one medication, 44% of patients are nonadherent; with two to three, that number rises to 58%; 77% of those using four or more medications are nonadherent to at least one of their treatments and 20% are nonadherent to the majority of their medications.

*https://www.cihi.ca/en/drug_spend_drivers_en.pdf

**https://www.benefitscanada.com/news/prescription-drug-spending-in-canada-to-hit-33-7b-in-2018-report-121979

- Perhaps not surprisingly, in light of the figures above, the top 20% of plan members (ranked by spending) account for almost 80% of total spending. These members struggle with the complexity of treating their chronic conditions, and their annual spending is, on average, $3,485, which is 15.6 times that of other members. They have an average of 5.7 conditions (compared to 2.5 for typical members), an average of 3.7 prescribers and an average of 8.6 medications.
- Our research aligns with many studies showing that patients with other chronic conditions are more likely to use a medication for mental health. Overall, one in four claimants (24.7%) is using a mental health therapy. However, almost 6 in 10 multiple sclerosis (MS) patients (57%) and about one in three cancer, asthma and diabetes patients use at least one mental health medication.

SUMMARY

With increasing drug costs and Canada's aging population, benefit plan sustainability depends on effective, individualized care that empowers members to choose their best treatment options.

The Papadopolous family's experience illustrates the power of a personalized, holistic approach to care, which makes it possible to cost-effectively deliver needed treatment. Even within a swiftly evolving pharmacy landscape, the benefits are clear:

FOR PLAN MEMBERS:

- Targeted, proven tools to assist individuals throughout their life span, from childhood to retirement and beyond.
- Tailored solutions, when and where they're needed.
- Assistance for families, helping them to efficiently manage their prescription drug treatments, which make up the major portion of privately funded healthcare spending.

FOR PLAN SPONSORS:

- Reduction in spending to maintain the sustainability of the drug benefits that are so highly valued by employees, while supporting productivity and engagement.

At Express Scripts Canada, our retrospective "big data" analysis goes beyond even the most recent science to tell us what tools really make a difference for members and their families. By starting with clinical evidence, we can help family decision-makers resist market forces – to choose the very best care for their family.

To ensure access to treatment and benefit sustainability in the years ahead, a 360-degree approach to care is essential. With our plans, our partners, policy makers and the supply chain, we can work together to ensure Canadians receive the healthcare they need.

"To ensure access to treatment and benefit sustainability in the years ahead, a 360-degree approach to care is essential."

METHODOLOGY AND TERMINOLOGY

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- DRUG TREND REPORT METHODOLOGY

DRUG TREND REPORT METHODOLOGY

Express Script Canada's **drug trends** measure the rates of change in the **gross cost per claimant**, which includes the **eligible drug cost** as well as the **eligible dispensing fee**. **Gross cost** includes the member's portion of the eligible cost as well as the plan sponsor's portion of the eligible cost. **Claimant** includes each unique individual with a prescription, including all dependents who are eligible for coverage.

Total trends comprise the utilization trend and cost per prescription trend. **Utilization trends** are the rates of change in the number of eligible prescription drug claims per claimant. **Cost per prescription trends** are the rates of change in eligible cost per prescription. Only claimants who were continuously eligible for coverage throughout the course of the year were included. Claimants who were not eligible for coverage throughout the entire calendar year were excluded from the analysis.

Please note: Express Scripts Canada's drug trend is based on a **retrospective** or historical methodology – a look back at the past. In this way, it differs from an insurance carrier's health plan premium increase, which is based on a **prospective** methodology. An insurance carrier's health plan premium increase incorporates data trends to anticipate future costs including a drug plan's specific claims experience, changes in proportion of eligible members with a claim, demographic changes, anticipated changes in the future mix of drugs, any erosion of member contributions, a risk component, and other health plan claims experience. As a result, Express Scripts Canada's trend factor will typically be lower than an insurance carrier's predicted average increase for extended healthcare plans, of which prescription drugs are only one component.

ADHERENCE

Adherence was calculated using the medication possession ratio (MPR), which is the sum of the days' supply for all fills of oral medications in a particular period, divided by the number of days in the period, for any patient with three or more fills of the drug during the period. Patients with an MPR of less than 0.8 or 80% were considered nonadherent.

TERMINOLOGY USED IN THIS REPORT

MEDICATION GROUPINGS:

- **Therapy class:** A grouping of medications based on their most common indication.
- **Specialty drugs:** Medications used to treat chronic, complex conditions such as severe rheumatoid arthritis, multiple sclerosis and cancer. Specialty medications include injectable and non-injectable drugs and have one or more of the following qualities: frequent dosing adjustments and intensive clinical monitoring; intensive patient training and compliance assistance; limited distribution; and/or specialized handling or administration.
- **Traditional drugs:** Medications that are easy to self-administer and require less intensive clinical monitoring, such as those used to treat diabetes and high blood pressure.

OVERALL TERMINOLOGY:

- **Spending:** Total cost of eligible prescription drugs, including the plan member's portion as well as the plan sponsor's portion net of any Product Listing Agreement discounts.
- **Claimant, Member or Patient:** Each unique person who submits a prescription drug claim, including all dependents who are eligible for coverage.
- **Trend:** The historical increase in cost per member over the previous year, which includes the eligible drug cost as well as the eligible dispensing fee. The total trend is made up of:
  - **The utilization trend:** The rate of change in the number of eligible prescription drug claims per member.
  - **The cost/Rx trend:** The rate of change in eligible cost per prescription drug claim.

INSIGHTS INTO CHALLENGES AND

OPPORTUNITIES

INSIGHTS INTO CHALLENGES AND OPPORTUNITIES

- DRUG SPEND PER CLAIMANT
- SUPPORT AND SOLUTIONS – THE PRINCIPLES OF APPLYING DRUG BENEFIT SOLUTIONS
- PATIENT INSIGHTS
- SUMMARY

When we first began reporting on drug trends 20 years ago, the prescription drug market was dramatically different than it is today. The era of blockbuster drugs – drugs formulated to treat millions of people with common conditions – was just taking off. That wave of development represented one of the first major challenges to sustainable prescription drug coverage. In 1998, prescription drug spending in Canada outside hospitals was $8 billion*. In 2018, that number was expected to reach $33.7 billion**, the culmination of a trend that far outpaced broader inflation.

In the past few years, wider adoption of plan design that empowers plan members and policy leadership on drug prices have contributed to a welcome reprieve in the trajectory of the overall trend.

At the same time, we have now entered an age of million-dollar-per-treatment drug launches and emerging gene therapies. Innovations that deliver potentially breakthrough treatments with stratospheric prices require us to be equally innovative in how we manage medications.

To ensure access to treatment and benefit sustainability in the years ahead, a 360-degree approach to care is essential. With our plans, our partners, policy makers and the supply chain, we can work together to ensure Canadians receive the healthcare they need.

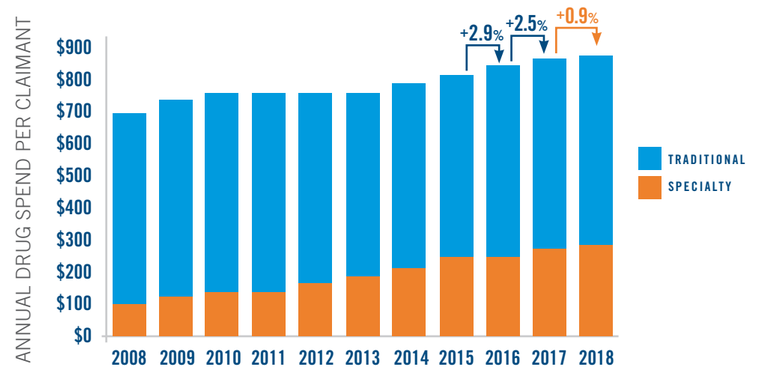
*https://www.cihi.ca/en/drug_spend_drivers_en.pdf

**https://www.benefitscanada.com/news/prescription-drug-spending-in-canada-to-hit-33-7b-in-2018-report-121979

DRUG SPEND PER CLAIMANT

NATIONAL DRUG TREND

INCREASE IN DRUG SPEND PER CLAIMANT SLOWED IN 2018 ...



In 2018, we saw the rate of growth in drug spending per claimant slow down to an increase of 0.9% over 2017, compared to 2.5% and 2.9% in the prior two years.

OHIP+ IMPACT ON TREND

OHIP +: CHILDREN AND YOUTH PHARMACARE

OHIP+: Children and Youth Pharmacare (OHIP+) is an Ontario government provincial drug coverage program that provides free prescription drug coverage for individuals 24 years of age and under. OHIP+ provides drug coverage under the Ontario Drug Benefit (ODB) program regardless of family income at no cost, with no co-payment or annual deductible. Enrollment in OHIP+ is automatic based on age for all infants, children and youth with an Ontario health card number.

OHIP+ coverage **started** on **January 1, 2018**. As of **April 1, 2019**, OHIP+ changed for those individuals

with access to private drug plan coverage. For those with a private plan, access to prescribed medications returns to the state that existed prior to the launch of OHIP+ on January 1, 2018; that is, they are **no longer eligible for OHIP+** coverage but instead are required to submit prescription drug claims to their private drug plan. Individuals and families with significant out-of-pocket costs, despite having a private drug plan, can apply for additional financial support through the Trillium Drug Program.

OHIP+ was implemented in Ontario on January 1, 2018. As a result, we saw a 63% drop in claims for those under age 25 versus the previous year with:

- A lower number of claimants. In 2017, 24% of all claimants in Ontario were under age 25. This dropped to 18% in 2018.
- Fewer claims per claimant for those under 25. In 2017, 9.1% of claims in Ontario were for members under age 25. This dropped to 4.3% in 2018.

The overall result was a 52% reduction in spend by this demographic, with a significant impact on overall drug spend.

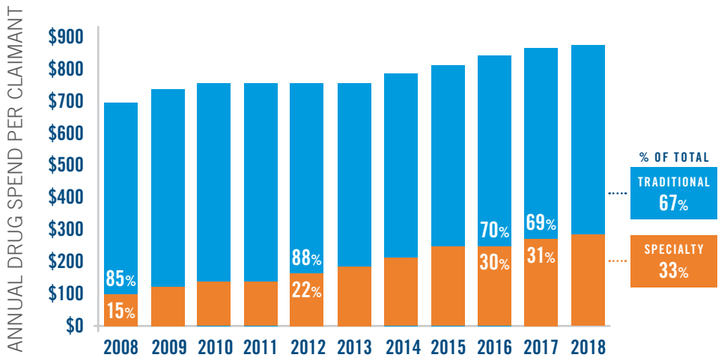
If OHIP+ had not been introduced, the increase in overall spending in 2018 would have been closer to 2.8%, in line with the previous two years.

In 2019, we will see a reversal of this impact, as the province's new government has redesigned OHIP+ to remove coverage eligibility for those with access to private drug plan coverage, effective on April 1.

SPECIALTY SPENDING CONTINUES TO GROW AT A DRAMATIC RATE

NATIONAL DRUG TREND

… HOWEVER SPECIALTY CONTINUES TO GROW AT A DRAMATIC RATE



This breakdown between specialty and traditional drug spending shows specialty's upsurge from 15% of total spending in 2008 to 30% in 2016, to 33% in 2018. With a high proportion of specialty drugs in the development pipeline, this trend is expected to continue, which we will review in more detail later.

The specialty versus traditional spending breakdown varies by province. In the western "pharmacare" provinces such as British Columbia, the provincial plans provide a significant amount of coverage, so specialty drugs represent a much lower proportion of private plan spending. In contrast, in the Atlantic provinces, where the provincial drug plan is the payor of last resort, specialty drugs make up a greater portion of private spending. (In the United States, where private plans are paying the full amount of specialty drug spending, specialty drugs represent 45% of spending.)

CHALLENGES REVEALED

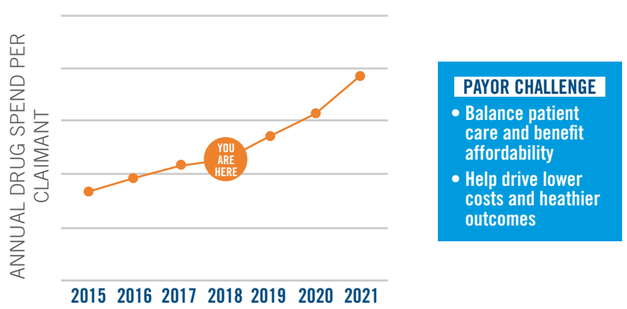
1. COST/SUSTAINABILITY

Growth in new high-cost therapies continues to be a primary spending driver. These drugs dominate the development pipeline, and the number of disorders for which they are approved continues to expand. As a result, balancing patient care and plan sustainability is an ongoing, increasing challenge for plan sponsors.

Employers and plan sponsors will continue to face the challenges of supporting costly novel therapies.

OUTLOOK ON FUTURE DRUG SPEND

GROWTH IN NEW HIGH-COST THERAPIES WILL CONTINUE TO DRIVE FUTURE BENEFIT COSTS



To make funding available for these costly but lifesaving therapies without threatening plan sustainability, plan members need effective, timely support. Within today's highly complex pharmaceutical landscape, most plan members don't have the knowledge or time they need to make the best decisions. Instead, marketplace forces make it likely their choices will increase plan and out-of-pocket spending significantly, without improving health outcomes.

2. ADHERENCE TO THERAPY

Adherence to medication is generally defined as the extent to which patients take medications as prescribed by their healthcare providers. This term is preferred to the older terminology of compliance, which suggests a more passive role for patients, following "doctor's orders" rather than following a treatment plan developed jointly by the patient and the physician.

The full benefit of medications can only be achieved if patients follow prescribed regimens. Yet a 2015 Canadian survey found that 30% of patients stopped taking a drug before they were advised to do so; 26% took less medication than they were instructed to take; 26% did not fill a prescription they were given by their healthcare provider. Only 12% of those not filling a prescription and 8% of those not taking their medication as prescribed stated that affordability was a factor in their nonadherence. This means that there are other factors that are causing nonadherence.

Nonadherence leads to spending waste. The aphorism attributed to former U.S. Surgeon General C. Everett Koop continues to hold true: "Drugs don't work in patients who don't take them," and is equally true of patients who don't take drugs as directed. Treatments already purchased are less effective or ineffective; worsening conditions mean additional and often more costly therapies may be needed.

Medication adherence can be assessed in a number of different ways. The most common are:

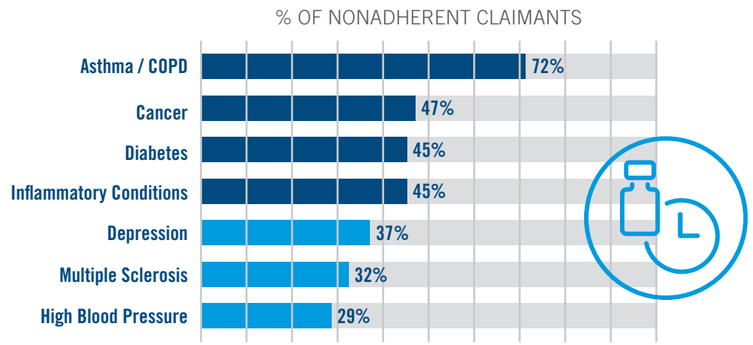
- Monitoring patient behaviours (e.g., electronic detection of a dose of a medication being administered);
- Patient self-reports (e.g., surveys);
- Pharmacy claims data.

With access to immense claims data, we use a metric known as Medication Possession Ratio (MPR). With this indirect, non-invasive approach, we cannot know if patients take the medication they have on hand, but we know with 100% certainty they cannot take medication they do not have. Patients with an MPR < 80% are considered to be nonadherent, as they have not purchased enough medication to be adherent.

POOR ADHERENCE ACROSS DRUG THERAPY CLASSES

NONADHERENCE BY THERAPY CLASS

POOR ADHERENCE OBSERVED ACROSS SEVERAL CLASSES



- Our research determined that over 70% of plan members with asthma or COPD were not adherent.
- High levels of nonadherence were also identified among members being treated for cancer (47%), diabetes (45%) and inflammatory conditions (45%).
- 37% of patients with depression, 32% with multiple sclerosis and 29% with high blood pressure were not adherent with at least one of their medications.

The causes of nonadherence are complex and multidimensional, involving the patient, healthcare provider, drug and health system.

Our claims analysis reveals that one patient factor that increases nonadherence is the use of multiple medications.

NONADHERENCE TO THERAPY

CLAIMANTS USING MULTIPLE MEDICATIONS ARE MORE LIKELY TO BE DEEMED NONADHERENT

	% OF NONADHERENT CLAIMANTS TO AT LEAST ONE MEDICATION	% OF NONADHERENT CLAIMANTS TO THE MAJORITY OF THEIR MEDICATIONS
CLAIMANTS USING 1 MEDICATION	44%	44%
CLAIMANTS USING 2-3 MEDICATIONS	58%	25%
CLAIMANTS USING 4+ MEDICATIONS	77%	20%

- 44% of claimants using one medication are nonadherent;
- 58% of claimants using two to three medications are nonadherent to at least one of their treatments; and
- 77% of claimants using four or more medications are nonadherent to at least one of their treatments.

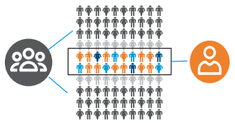
Of greatest concern is the 20% of claimants who use more than four medications and who are nonadherent to the majority of their medications, illustrating the links between treatment complexity and gaps in care. This has the potential to accelerate spending increases in this more vulnerable patient population.

3. MANAGING TREATMENT COMPLEXITY

The top 20% of plan members (ranked by spending) account for almost 80% of total spending.

80/20 RULE

TOP 20% OF CLAIMANTS, WHICH ACCOUNT FOR 79% OF SPEND, FACE HIGHER LEVELS OF COST AND COMPLEXITY



		TYPICAL CLAIMANT	TOP 20%
		80% / 21% TOTAL CLAIMANTS / TOTAL SPEND	20% / 79%
ANNUAL COST	AVG PER CLAIMANT	$223	$3,485
# OF CONDITIONS	AVG PER CLAIMANT	2.5	5.7
# OF PHYSICIANS	AVG PER CLAIMANT	2.0	3.7
# OF UNIQUE MEDICATIONS	AVG PER CLAIMANT	3.1	8.6
% OF CLAIMANTS USING SPECIALTY		0.7%	12%

These members struggle with the complexity of treating their chronic conditions, and their annual drug spending is 15.6 times that of other members, an average of $3,485.

THEIR CHALLENGES INCLUDE MANAGING:

- Multiple chronic conditions – an average of 5.7 medical conditions compared to 2.5 for typical members;
- The coordination of care provided by multiple physicians – an average of 3.7 prescribers compared to 2 for typical members;
- Multiple medications – an average of 8.6, almost three times more than typical members (with 3.1 medications).

Unsurprisingly, these challenges lead to greater levels of nonadherence.

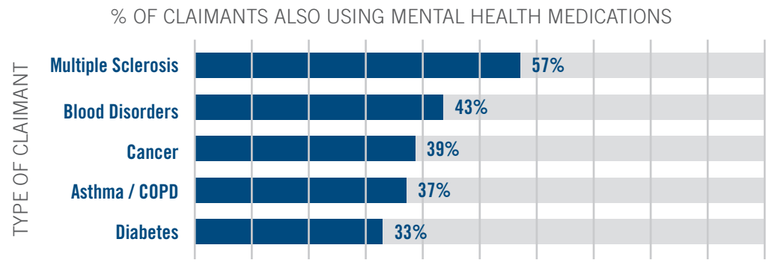
These members are also more likely to use specialty medications, and need help managing the treatment complexity inherent with this type of drug therapy. However, our data analysis makes it clear that members in the top 20% by spending struggle and need individualized support even if all their medications are in the traditional category.

4. THE BODY-MIND CONNECTION

Our research aligns with many other studies showing that patients with other chronic conditions are more likely to use a medication for mental health. These include medications for depression and other mood disorders, anxiety, sleep disorders, and antipsychotic medications. Overall, one in four claimants (24.7%) are using a mental health therapy. This is higher in Quebec (28.4%) than in the rest of Canada (23.5%). However, claimants with chronic medical conditions such as MS, cancer and diabetes have a notably higher use of mental health medications.

MENTAL HEALTH

PATIENTS WITH CHRONIC CONDITIONS ARE MORE LIKELY TO USE MENTAL HEALTH MEDICATIONS

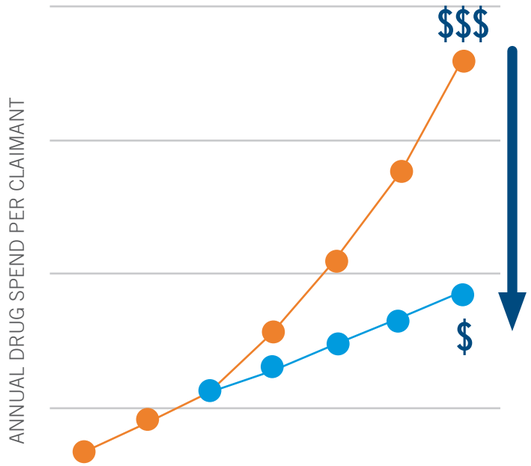


- Almost 6 in 10 multiple sclerosis patients (57%) use at least one mental health medication;
- More than 4 in 10 blood disorder patients use at least one mental health medication; and
- More than 1 in 3 cancer and asthma patients and 1 in 3 diabetes patients use at least one mental health medication.

SUPPORT AND SOLUTIONS – THE PRINCIPLES OF APPLYING DRUG BENEFIT SOLUTIONS

TOOLS TO MANAGE SPEND

COMPREHENSIVELY MANAGED PLANS CAN BEND THE CURVE ON DRUG SPENDING



COMPREHENSIVELY MANAGED PLAN TOOLS:

Formulary management
Provide access to clinically effective medications while targeting high-cost therapies that offer no added clinical benefit.

Utilization management
Use of tools such as prior authorization (PA) and step therapy programs to guide patients to safer, more cost-effective drug choices and to ensure the right drug is provided to the right patient, by the right payor, at the right time.

Channel management
Leveraging a network of preferred pharmacies to drive down costs while delivering better patient care.

Patient health management
Specialized holistic care can help patients better manage treatment complexity to achieve lower costs and healthier outcomes.

Our data analysis and research make it clear that, to maintain benefit sustainability, manage their out-of-pocket spending and achieve optimum health outcomes, plan members need help. In the face of time pressure and a complex healthcare system, this help must be clinically informed and delivered at the right time.

Comprehensively managed plans use a full menu of managed plan tools to improve care and bend the curve on drug spending. These tools can help address the challenges of cost, adherence, complexity and gaps in treatment. Plan design starts with a clinical approach – that is, first applying clinical guidelines and the latest health research – overlaid with a proactive approach to managing market conditions. This two-pronged approach leverages the impact of benefit management tools, including formulary management, utilization management, channel management and patient health management, as follows:

1. **Formulary Management** – Uses an **actively managed drug benefit formulary** to provide enhanced access to the most clinically effective medications, while targeting high-cost therapies that offer no additional clinical benefit. This is further enhanced by a patient-accessible, web-based tool that assists members in understanding the costs of their medications and the cost-effective alternatives available.

2. **Utilization Management** – Using tools and programs to ensure that the right drug is provided to the right patient, at the right time, and is paid for by the right plan. Utilization management tools include:

   - **Prior Authorization (PA)** – Manages higher-cost drug claims to ensure that these therapies are used by the most clinically appropriate patients;

   - **Step Therapy Program** – An automated tool that ensures that the most cost-effective therapies are used first, before less cost-effective options.

3. **Channel Management** – Uses a network of preferred pharmacies to drive down costs while delivering optimal patient care. These tools include:

   - **A Pharmacy Value Finder** – Patient-accessible web-based tool to assist members in finding the lowest-cost retail pharmacy in their area and plan network;
   - **Home Delivery of Maintenance Drugs** – Delivery of three-month supplies of regularly used drugs for chronic medical conditions, with auto-refill capability, to help improve adherence while lowering costs; and
   - **Specialty Pharmacy** – Providing a full range of patient-focused clinical and operational services to enhance the safety, quality and affordability of care for patients using specialty drugs.

4. **Patient Health Management** – Providing specialized, holistic care to help patients better manage treatment complexity, lowering costs and improving health outcomes. This includes access to a Therapeutic Resource Centre, with pharmacy specialists who provide patient-focused consultation to assist in the management of chronic diseases and the medications prescribed for them.

A PERSONALIZED, HOLISTIC APPROACH TO CARE

Just like their fingerprints, the health and healthcare needs of every individual are unique to them. Our research reveals that, to be fully effective, plan management tools must help patients on a personal level.

To realize the full benefits of drug treatment plans, the focus of care must shift from treatment to the whole patient. This also means closing gaps in care, especially among members who have more than one chronic condition and multiple physicians.

Proactive pharmacy and claims processing design lessens the risk that members may take one or more medications inappropriately, helping to ensure safety and adherence across their treatment regimen, and reducing duplications.

A 360-degree view of patient health drives a 180-degree change in health outcomes, by shifting from a reactive system to a proactive, holistic approach to health and disease management.

PATIENT INSIGHTS

COMPREHENSIVE BENEFIT MANAGEMENT IN ACTION
THE PAPADOPOULOS FAMILY*

THE PAPADOPOULOS FAMILY

Like many Canadian families, the Papadopoulos family is multigenerational. Helen and her husband John have three young boys, and Helen's parents live with them in a downstairs suite.

WITHIN THE FAMILY, THE HEALTHCARE NEEDS ARE DIVERSE:

- Helen is taking a medication for low thyroid function;
- John has a painful inflammatory condition called ankylosing spondylitis (AS);
- Alex, the middle child, has asthma;
- Helen's father, Gus, lives with diabetes.

As each member of the Papadopoulos family has unique health and healthcare needs, a personalized and holistic approach is required.

*The Papadopoulos family is a fictional representation of a typical Canadian multigenerational family.

MOM – HELEN

Helen is the primary caregiver for her family. Everyone counts on her to prepare family meals, including lunches for school and work. Like many parents whose spouses bring in the lion's share of the family income and don't have much flexibility in their day, Helen is in charge of making sure everyone in the family keeps their medical appointments and takes any prescribed medication. With three boys (Jason, Alex and Chris), Helen is also the chief activity officer, driving the kids to and from soccer and hockey and making sure they're registered, equipped and appropriately cheered. And if that isn't enough to make you tired, Helen also works full time.

HELEN'S PRIMARY HEALTH CHALLENGES

Helen has hypothyroidism, which is treated with levothyroxine. She's been using it for over a year. But like most primary caregivers, Helen tends to put herself and her health last on her priority list. She frequently misses doses – in fact, it happens three or four times a week, meaning that her thyroid condition is not well-controlled.

She's felt better since she started taking levothyroxine but has been late to order her refills for each of the last three months and has missed doses as a result. Lately, she has been feeling fatigued, especially in the afternoons, but chalks it up to the additional stress she's coping with at work and with her dad.

She's embarrassed about missing her medication and therefore doesn't mention it to her doctor, only saying that she's tired.

Helen needs help to stay on track with her medication, feel better and have more energy to manage her busy life. She is experiencing **unintentional nonadherence**.

COMPREHENSIVE PLAN OPPORTUNITIES

Channel management, via the implementation of a Home Delivery program, can help ensure that Helen's prescription is refilled before she runs out.

- Receiving a three-month supply of medication directly to her home means she doesn't have to find time to drive to a pharmacy to pick up her prescription each month.
- An auto-refill service means she doesn't have to rely on her memory to get her refills on time.
- By moving from a one-to-three-month supply, dispensing costs are reduced, and two items are taken off Helen's epic to-do list.

Ensuring that Helen has medication on hand when she needs it allows her to stay adherent. The result is a better health outcome – she feels better and has more energy to manage her busy life.

MEET HELEN ...

38-YEAR-OLD MOTHER OF THREE BOYS.
- Primary family caregiver
- Managing activities of children
- Works full time outside of the home

HAS LOW THYROID HORMONE LEVELS

CHALLENGE

Helen is struggling with adherence:

- Remembering to pick up her thyroid medication at the pharmacy each month.

OPPORTUNITY

- Formulary Management
- Utilization Management
- **Channel Management**
- Patient Health Management

DESIRED OUTCOME

LOWER COSTS + HEALTHIER OUTCOMES

DAD – JOHN

John is his family's primary income earner. He has been treated for depression and high blood pressure for the past three years. His medications include:

- For depression: sertraline 25 mg once a day – prescribed and monitored by his psychiatrist;
- For high blood pressure: amlodipine 10 mg once a day – prescribed and monitored by his cardiologist.

JOHN'S PRIMARY HEALTH CHALLENGES

John is a maintenance electrician, which involves hard physical labour, crawling in small spaces, and many repetitive motions. When he started to experience low-back pain last year, he first assumed he'd hurt something at work and tried to treat the pain with over-the-counter anti-inflammatories.

Recently, John's family doctor recommended that John be evaluated by a rheumatologist, suspecting that he may actually have an inflammatory condition rather than simple chronic back pain. The rheumatologist diagnosed John with ankylosing spondylitis (AS) and prescribed the specialty medication Enbrel, which John self-injects.

John needs help understanding his diagnosis and the prescribed treatment. With multiple chronic conditions (depression, high blood pressure and ankylosing spondylitis) and prescribers, John is at high risk of nonadherence, gaps in care, worsening health and unnecessary medication spending.

COMPREHENSIVE PLAN OPPORTUNITIES

Utilization Management via Prior Authorization

- Enbrel (etanercept), along with other biologic disease modifying anti-rheumatic drugs (DMARDs), is managed with Prior Authorization, which helps ensure the right patients get the right drugs at the right time. As part of the prior authorization process, a step therapy protocol ensures that John has used another therapy before using etanercept.
- Prior Authorization can also point John towards biosimilars for Enbrel (Brenzys and Erelzi), which provide equivalent effects at lower cost, particularly for individuals new to therapy. These are recommended for use before approval of Enbrel.

Channel Management via a Specialty Pharmacy Program

A Preferred Provider Network with a Specialty Pharmacy can help John and other patients like him:

- Lower plan and out-of-pocket drug costs through a mark-up cap (fixed-dollar maximum versus percentage of dollar costs with no maximum);
- Control dispensing fees; and
- Manage adherence by using home delivery and reminders to ensure that he has his medication on hand when he needs it, without exception.

John has access to **Reimbursement Navigation Advocate Services** through his use of the Specialty Pharmacy. The Advocate Services specialist facilitated completion of the Prior Authorization form and assisted John in obtaining secondary coverage assistance with his share of the high prescription cost.

For families with tight budgets and full calendars like John's, this can be a game changer. The service helps members find complementary and alternative forms of funding and reimbursement, lightening the burden on their personal finances as well as their plan. This may include integration with public programs, such as the Trillium Drug Program in Ontario, and coordination of benefits with other private drug plans if available. It also helps members complete prior authorization forms to avoid the delays and frustration that can result when vital information is left out.

Patient Health Management via Specialized Pharmacists

John's Specialty Pharmacy program also gives him access to Therapeutic Resource Centre pharmacists and a Specialty Pharmacy Case Manager, who provide clinical counselling to help John take his medication as directed, manage side effects and help him manage his medical appointments (including lab tests and follow-ups). Together, they can:

- Train John in self-administering his treatment by subcutaneous injection;
- Provide the counselling he needs, including side effect management and encouragement;
- Assist with the challenges inherent in managing multiple medications for multiple chronic diseases from multiple prescribers, such as drug interactions;
- Reach out to prescribers when needed to optimize John's therapy.

John is facing many challenges within his complex health situation. He needs assistance managing his multiple conditions, numerous physicians, and the use of a new high-cost specialty drug. Many of the tools available through his comprehensively managed drug plan will prove to be extremely valuable.

The Therapeutic Resource Centre pharmacists will continue to provide John with assistance in managing use of his new specialty medication, and he will be monitored for adherence.

MEET JOHN …

40-YEAR-OLD FATHER OF THREE BOYS.
- Primary income earner
- Works as a maintenance electrician

IS BEING TREATED FOR DEPRESSION AND HIGH BLOOD PRESSURE

RECENTLY DIAGNOSED WITH **ANKYLOSING SPONDYLITIS (AS)** BY HIS RHEUMATOLOGIST

CHALLENGES

- John needs help understanding the latest diagnosis by his rheumatologist and the corresponding specialty medication treatment that was prescribed (Enbrel).
- John needs help managing multiple chronic conditions, multiple prescribers.

OPPORTUNITY

- Formulary Management
- Utilization Management
- Channel Management
- Patient Health Management

DESIRED OUTCOME

LOWER COSTS + HEALTHIER OUTCOMES

SON – ALEX

Helen and John's son, Alex, is 11 years old and has had chronic asthma since he was eight.

His treatment is:

Maintenance with a regularly dosed daily low-dose inhaled corticosteroid (ICS), **Alvesco® Metered-Dose Inhaler (MDI)** 100 mcg ("controller" inhaler) one puff daily, plus **salbutamol HFA MDI** (a "rescue" inhaler) 100 mcg one to two puffs as needed. (The maximum daily dose for someone Alex's age should be four puffs per day; thus, one 200-dose MDI should last 50 days.)

ALEX'S PRIMARY HEALTH CHALLENGES

Alex is experiencing frequent asthma symptoms – his asthma is not well-controlled. He is underusing his controller therapy (Alvesco), which he should be using every day, and overusing his rescue therapy (salbutamol), which should be rarely required.

The family's claims records show that Alex's Alvesco has not been refilled in six months and that his Salbutamol has been refilled monthly for the last four months.

Alex is nonadherent and his health is suffering as a result.

COMPREHENSIVE PLAN OPPORTUNITIES

Channel Management via Preferred Provider Network Home Delivery Pharmacy

- Monitors Alex's medication adherence;
- When nonadherence is revealed, a pharmacist reaches out to Alex's mom to let her know his controller medication is not being refilled as needed and his rescue medication is being refilled too frequently.

Patient Health Management

Since Alex's mom is filling his inhalers through the Home Delivery pharmacy, she has access to the Therapeutic Resource Centre, which includes a pharmacist trained in respiratory education. She reaches out to Helen to discuss Alex's condition as well as the use of inhalers.

Helen shares her concerns about the possible side effects of "long-term steroid use," especially the potential for growth suppression, so the pharmacist provides information on the benefits of Alex's control therapy versus the risks. This is an example of **intentional nonadherence**, which usually requires a form of behavioural intervention. Patient health management delivered by the Therapeutic Resource Centre pharmacist fits the bill. By the time she hangs up, Helen understands that Alex's asthma symptoms can be completely controlled if he uses his control medication as directed – that is, he might never have to use his rescue inhaler.

Research tells us that there are many different reasons for being nonadherent, some clinical, some cost-related and some behavioural – so improving adherence requires a highly personalized approach.

While both Helen and Alex were nonadherent, Helen wasn't taking her medication as directed because it was difficult for her to pick up (unintentional nonadherence). Alex wasn't using his medication as directed because his mom had unaddressed, natural concerns about potential side effects (intentional nonadherence). These two different primary causes of nonadherence require different plan management tools to resolve them.

Through channel management and patient health management, we can achieve lower costs and healthier outcomes including:

- Improved asthma control for Alex, with prescribed use adherence for controller inhaler;
- Decreased use of rescue inhaler;
- Preserved lung function over the long term;
- Increased ability for Alex to participate in daily activities (such as sports).

MEET ALEX ...

11-YEAR-OLD CHILD

ASTHMA

- Requiring maintenance medication
- Experiencing daily symptoms

CHALLENGE

- Alex struggles with continuing asthma symptoms due to underuse of controller therapy and overuse of rescue therapy.

OPPORTUNITY

- Formulary Management
- Utilization Management
- Channel Management
- Patient Health Management

DESIRED OUTCOME

LOWER COSTS + HEALTHIER OUTCOMES

GRANDDAD – GUS

Gus is a 63-year-old retiree who, with his wife Georgia, lives with their daughter Helen and her family. He was recently diagnosed with type 2 diabetes. He has private retiree drug coverage, but the annual maximum is low, with coverage of $1,000 per year.

Gus's doctor prescribed Onglyza (10 mg once daily) to lower his blood glucose. Gus also takes Pravastatin (80 mg, two 40 mg tablets, once daily) for his high cholesterol and has been taking it for the past three years.

GUS'S PRIMARY HEALTH CHALLENGES

Gus's challenge is managing the costs of drug therapy despite his plan's $1,000 coverage cap. In addition, he is concerned about the effects of diabetes and its long-term impact on his health. He is especially worried about the potential complications he has heard about, specifically blindness, amputation and kidney failure.

Even with limited drug benefit coverage, there are simple tools that can be used, beyond annual benefit caps, to help manage drug benefit costs, while providing plan members access to cost-effective therapies that drive positive health outcomes.

COMPREHENSIVE PLAN OPPORTUNITIES

Formulary Management

Gus's managed formulary can direct him towards the use of the most cost-effective therapies by providing higher reimbursement for more cost-effective drugs. Cost-effective therapy choices also lead to lower out-of-pocket costs for plan members.

Gus calculates the costs of the new drug prescribed for diabetes in addition to his therapy for high cholesterol and sees that the plan portion alone will exceed his annual limit. Gus wants to know if there are alternatives that can bring his costs in line with his drug plan's ceiling.

- His newly prescribed diabetes drug therapy, Onglyza, is a Tier 2 drug. The total cost of one month of treatment is $111. Gus's plan pays 60% co-insurance for a Tier 2 drug, leaving Gus with an out-of-pocket cost of $44.
- His high cholesterol drug therapy, Pravastatin, is also a Tier 2 drug. The total cost of one month of therapy at 80 mg per day is $27; Gus's plan pays $16, and Gus pays $11. Until now, it wasn't a concern since it was Gus's only drug spending.

Patient Health Management via Disease Case Management

Gus knows very little about managing his diabetes, and because he doesn't want to be a bother to his doctor, doesn't ask many questions. But Gus has access to a Disease Management program, including a pharmacist trained in diabetes education who provides advice and explains the alternatives for diabetes and high cholesterol treatment.

- Diabetes – The pharmacist informs Gus that metformin, recommended by the Diabetes Canada Clinical Guidelines as the first-line drug for lowering blood glucose, is on the top reimbursement tier of his formulary (Tier 1). Together, they review the cost using Gus's plan's Drug Look-Up feature and see that the total cost for one month (metformin 2,000 mg per day [4 x 500 mg]) is only $16, of which Gus would only have to pay $2.
- High Cholesterol – The pharmacist advises Gus that a drug called rosuvastatin provides a more potent cholesterol-lowering effect, is on Tier 1 of the formulary, and could allow Gus to achieve his blood cholesterol target with a lower dose. Using Drug Look-Up, Gus and the pharmacist see that one month of rosuvastatin 5 mg (an equivalent to Gus's current pravastatin dose) would cost a total of only $17; Gus's out-of-pocket cost would be just $2.

The pharmacist reassures Gus that he can effectively manage his diabetes within the limits of his drug plan. By keeping his blood sugar levels under control, he can reduce his risks of the long-term complications he is naturally concerned about. The pharmacist refers Gus to the Diabetes Canada website and programs, drawing his attention to a patient-friendly explanation of the essentials of diabetes care, based on the Diabetes Canada Clinical Guidelines.

Gus's pharmacist also notes a potential gap in care: according to guidelines, Gus should be taking a vascular protection drug such as an ACE inhibitor or ARB.

As well, the pharmacist checks in with Gus to ensure he's being screened for the complications and conditions associated with diabetes, tracking eye exams (to help prevent blindness), foot exams (to help prevent neuropathy and infection), testing for kidney function, and by conducting the PHQ-9 questionnaire (obtaining baseline measurements and updating periodically) for depression and anxiety.

Formulary management and patient health management help lower spending by starting treatment with cost-effective alternatives. In addition to relieving the cost burden, these tools support better health outcomes, since better management of diabetes – treatment based on clinical guidelines – can delay and reduce the risk of complications.

MEET GUS ...

63-YEAR-OLD RETIREE

RECENTLY DIAGNOSED WITH TYPE 2 DIABETES

- Has been using high cholesterol medication for three years
- Has a retirement drug benefit plan with low annual maximum - $1,000/year

CHALLENGES

- Gus struggles with the cost of his medications.
- Gus is worried about his diagnosis.

OPPORTUNITY

- Formulary Management
- Utilization Management
- Channel Management
- Patient Health Management

DESIRED OUTCOME

LOWER COSTS + HEALTHIER OUTCOMES

SUMMARY

With increasing drug costs and Canada's aging population, benefit plan sustainability depends on effective, individualized care that empowers members to choose their best treatment options.

The Papadopolous family's experience illustrates the power of a personalized, holistic approach to care, which makes it possible to cost-effectively deliver needed treatment. Even within a swiftly evolving pharmacy landscape, the benefits are clear:

FOR PLAN MEMBERS:

- Targeted, proven tools to assist individuals throughout their life span, from childhood to retirement and beyond.
- Tailored solutions, when and where they're needed.
- Assistance for families, helping them to efficiently manage their prescription drug treatments, which make up the major portion of privately funded healthcare spending.

FOR PLAN SPONSORS:

- Reduction in spending to maintain the sustainability of the drug benefits that are so highly valued by employees, while supporting productivity and engagement.

At Express Scripts Canada, our retrospective "big data" analysis goes beyond even the most recent science to tell us what tools really make a difference for members and their families. By starting with clinical evidence, we can help family decision-makers resist market forces – to choose the very best care for their family.

"Comprehensively managed plans use a full menu of managed plan tools to improve care and bend the curve on drug spending. These tools can help address the challenges of cost, adherence, complexity and gaps in treatment."

A LOOK AT THE OVERALL DRUG TREND

FOR 2018

A LOOK AT THE OVERALL DRUG TREND FOR 2018

- OVERALL TREND IN 2018
- TRADITIONAL DRUG TREND OVERVIEW
- SPECIALTY DRUG TREND OVERVIEW
- TOP TEN MEDICATIONS BY SPENDING
- TOP 10 THERAPY CLASSES – INSIGHTS FOR 2018
- OTHER NOTABLE THERAPY CLASSES

OVERALL TREND IN 2018

For plan sponsors, protecting plan sustainability starts with an understanding of the high-level influences that affect benefit spending and the health of members. In 2018, as for each year since the launch of our first annual Drug Trend Report, Express Scripts Canada leveraged the vast amount of data involved in processing the claims of millions of Canadians to analyze these trends.

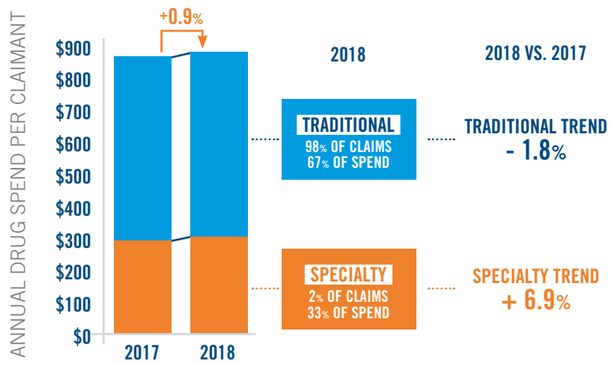
Private plan spending temporarily slowed in 2018, in part due to the implementation of OHIP+.

Nationally, the average annual drug spending per member increased by 0.9%, to $869.56, less than the spending increase of 2.5% in 2017.

The 2018 overall trend was made up of a 1.8% decrease in spending on traditional medications and an increase of 6.9% in spending on specialty medications.

TRADITIONAL VS. SPECIALTY

INCREASE IN SPECIALTY MASKED BY DECREASE IN TRADITIONAL

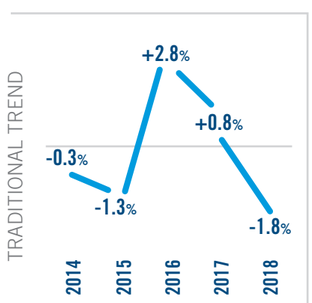


Of note: Traditional drugs made up 98% of drug claims in 2018 but only 67% of drug spending, while specialty drugs represented only 2% of 2018 drug claims but 33% of drug spending.

TRADITIONAL DRUG TREND OVERVIEW

TRADITIONAL DRUG TREND
DECLINE IN TRADITIONAL DRIVEN BY REDUCTION IN UTILIZATION

TRADITIONAL TREND -1.8% = **UTILIZATION -1.4%** + **COST/RX -0.4%**



FACTORS DRIVING TRADITIONAL TREND IN 2018

+ Introduction of new, higher-cost brands
+ Shift to higher-cost medications

– **Impact of OHIP+ in Ontario**
– Ongoing patent expirations
– pCPA negotiated generic prices
– Greater use of plan design controls

Traditional drugs are those used to treat common medical conditions such as diabetes, high blood pressure and depression. In 2018, 98% of the total number of benefit claims made were for drugs in this category. From a spending perspective, traditional drugs accounted for 67% of the 2018 total, down from 69% in 2017.

The last two years brought a welcome respite in the longer-term upward trajectory of spending in the traditional category. Following a flat trend in 2017, traditional spending declined by 1.8% in 2018 due to decreases in both utilization (1.4%) and cost per prescription (0.4%).

Contributing factors include OHIP+ changes that made more than 4,400 drugs free in Ontario for those 24 years old or younger. Another major factor was generic price reductions by the pan-Canadian Pharmaceutical Alliance (pCPA) that became effective on April 1, 2018. Prices for almost 70 of the most commonly prescribed generic drugs were reduced by 25% to 40%, representing discounts of up to 90% off the price of their brand-name equivalents.

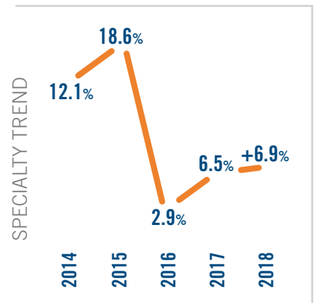
On the other hand, factors putting continued upward pressure on spending in this category included new higher-cost brands, as well as a shift toward higher-cost medications within therapy classes such as diabetes.

These factors, combined with the growing prevalence of these common conditions, have the potential to have a massive impact on private plan costs going forward. However, greater use of plan design controls such as generic substitution and managed formularies can help plans take advantage of the positive changes underway while managing the inflationary factors, to achieve overall sustainability.

SPECIALTY DRUG TREND OVERVIEW

SPECIALTY DRUG TREND
GROWTH IN SPECIALTY DRIVEN BY GREATER UTILIZATION

SPECIALTY TREND +6.9% = **UTILIZATION +6.1%** + **COST/RX +0.8%**



FACTORS DRIVING SPECIALTY TREND IN 2018

+ New high cost specialty medications
+ New indication approvals

– **Impact of OHIP+ in Ontario**
– Higher adoption of plan controls and PLAs
– Ongoing specialty patent expirations

Specialty spending continues to be a concern for private plan sponsors. Over the course of the last decade, spending in this category has more than doubled. In 2018, specialty drugs represented 33% of overall spending – despite representing just 2% of total claims.

A total increase of 6.9% in 2018 followed an increase of 6.5% in 2017. (Utilization increased by 6.1% and cost per prescription increased by 0.8% in 2018.)

The factors driving this steep increase included:

1. Higher utilization of specialty medications for conditions such as:
   a. Asthma, which until recently was treated only with traditional drugs; and
   b. Cancer, which was previously treated with hospital-administered injectable drugs covered by public health plans. The advent of specialty oral cancer drugs has driven much of this cost onto the private sector.
2. The introduction of new high-cost medications. Most drug development efforts are focused on filling the remaining treatment gaps, which require specialty medications.
3. New indication approvals for existing drugs, which expand the number of patients who may use these drugs.

The specialty spending trend was softened slightly by OHIP+ coverage and by a few patent expirations that helped reduce the increase in cost per prescription, as mentioned above in the traditional category analysis.

TOP 10 MEDICATIONS BY SPENDING

The three medications that led spending in 2018 were specialty drugs used to treat inflammatory conditions. Infliximab, adalimumab and ustekinumab made up more than 10% of the overall total.

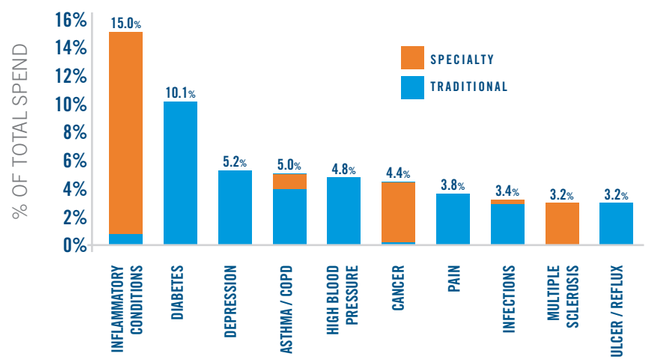
Traditional medications that treat diabetes, attention deficit disorder and high cholesterol also continue to make up a significant portion of overall spending.

TRADE NAME	CHEMICAL	COMMON INDICATION	CATEGORY*	% OF TOTAL SPENDING	RANK BY SPENDING
Remicade® / Inflectra® / Renflexis™	Infliximab	Inflammatory Conditions	S	4.62%	1
Humira®	Adalimumab	Inflammatory Conditions	S	3.76%	2
Stelara®	Ustekinumab	Inflammatory Conditions	S	1.67%	3
Contour Next®/ One Touch Verio®/ Others	Blood Glucose Test Strips	Diabetes	T	1.56%	4
Ritalin® / Concerta® / Biphentin® / Foquest™	Methylphenidate	Attention Deficit Disorder	T	1.52%	5
Janumet®	Sitagliptin/Metformin	Diabetes	T	1.37%	6
Victoza® / Saxenda®	Liraglutide	Diabetes / Weight Loss	T	1.34%	7
Enbrel® / Brenzys® / Erelzi™	Entanercept	Inflammatory Conditions	S	1.27%	8
Crestor®	Rosuvastin	High Cholesterol	T	1.12%	9
Lantus® / Toujeo™ / Basaglar™	Insulin Glargine	Diabetes	T	1.03%	10

*S = Specialty; T = Traditional

TOP TEN CLASSES BY SPEND

TOP TEN CLASSES DOMINATED BY TRADITIONAL SPEND



PREVALENCE (% OF CLAIMANTS)	1.3%	7.7%	14.8%	13.5%	17.4%	1.5%	27.6%	40.4%	0.1%	14.7%
COST PER CLAIMANT	$10,075	$1,121	$300	$309	$246	$2,449	$115	$69	$19,693	$190

TOP 10 THERAPY CLASSES – INSIGHTS FOR 2018

SPENDING RANK #1 – INFLAMMATORY CONDITIONS

Inflammatory conditions include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and Crohn's disease. The high cost per prescription within this class resulted in the largest single proportion of plan spending, 15%, despite being used by only 1.3% of members.

The 2018 trend for inflammatory conditions was driven by a 7.2% increase in utilization while the cost per prescription decreased slightly (0.6%).

Inflammatory condition drugs include both traditional and specialty medications. The traditional category includes medications for rheumatoid arthritis, such as methotrexate and Arava® (leflunomide) and inflammatory bowel disease treatments such as Mezavant® (mesalazine). Traditional drugs account for almost half of all claims (42%) but only 5% of total spending in this class.

In contrast, specialty drugs account for 95% of spending and 58% of claims.

Despite the availability of 16 specialty therapies to treat inflammatory conditions, two drugs (Remicade®/ Inflectra®/Renflexis™ (infliximab) and Humira® (adalimumab)) accounted for approximately 54.7% of spending.

Further developments within this class include new drug approvals and new indication approvals for existing drugs.

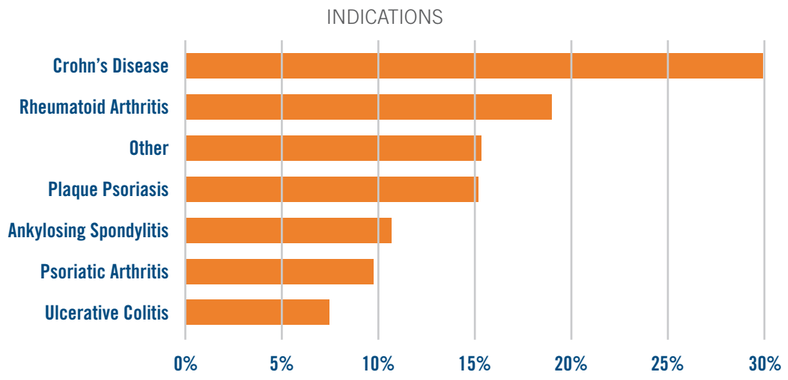
A new oral drug, Olumiant™ (baricitinib), was approved in 2018 for use in moderate to severe rheumatoid arthritis. Olumiant is similar to Xeljanz™ (tofacitinib) as it belongs to the same drug family, with comparable pricing. There are multiple treatment options available for rheumatoid arthritis, including specialty biologics with well-characterized efficacy and long-term safety.

A new biologic, Siliq™(brodalumab), was approved in 2018 for use in moderate to severe plaque psoriasis. Siliq is the third interleukin-17 inhibitor approved for psoriasis. The mechanism of action for Siliq, an interleukin-17 receptor antagonist, is distinct from the other drugs in this class, Cosentyx® (secukinumab) and Taltz™ (ixekizumab), which bind directly to cytokine IL-17A.

Many specialty drugs are approved for the treatment of multiple inflammatory diseases. New indications were approved in 2018 for several existing drugs, which contributed to an increase in overall utilization. These included:

1. Orencia® (abatacept) received approval for psoriatic arthritis. Orencia was previously only approved for adult rheumatoid arthritis and juvenile idiopathic and rheumatoid arthritis.
2. Simponi® I.V. (golimumab), previously indicated only for rheumatoid arthritis, received additional approval for psoriatic arthritis and ankylosing spondylitis.
3. Taltz® (ixekizumab) received approval for psoriatic arthritis. Taltz has an existing approval for plaque psoriasis.
4. Cimzia® (certolizumab pegol), formerly only approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, received additional approval for plaque psoriasis.
5. Xeljanz® (tofacitinib), previously approved only for rheumatoid arthritis, received approval for ulcerative colitis and psoriatic arthritis.
6. Humira® (adalimumab), formerly approved only for the treatment of hidradenitis suppurative in adults, received expanded approval for the treatment of adolescent patients between 12 and 17 years old weighing more than 30 kg. Humira is also approved for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis and uveitis.

Express Scripts Canada monitors the medical use (indication) requested through the Express Scripts Canada Prior Authorization Program. The bar graph on the next page shows the top treatment indications for drugs within the inflammatory condition class, based on prior authorization requests received from July to December 2018. Crohn's disease, rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, psoriatic arthritis and ulcerative colitis indications accounted for over 90% of requests.



Hadlima® (adalimumab), approved in 2018 but not yet available for sale, is the first biosimilar for Humira. (A biosimilar is a biologic drug demonstrated to be therapeutically similar to a brand name drug already approved, which is known as the reference or innovator drug.) Humira accounts for 25.9% of spending within this class. As biosimilars offer lower-cost alternatives and increased competition, Hadlima promises to provide significant savings. However, it is not expected to be immediately available in Canada.

Other biosimilars currently available in this class include: Inflectra®/Renflexis™ for Remicade® and Brenzys®/Erelzi™ for Enbrel®. In 2018, the biosimilars for Remicade and Enbrel accounted for 4.6% and 7.4%, respectively, of claims for their chemical ingredient. This is an increase from 2.0% and 1.5%, respectively, in 2017. The uptake of biosimilars may be reduced due to product listing agreements or manufacturer copay programs on the innovator product.

Increases in utilization, new drug approvals and expanding indications will continue to drive increases in spending for this therapy class. The availability of biosimilars will help mitigate this slightly.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
1	Inflammatory Conditions	15.0%	7.2%	-0.6%	6.6%

PREVALENCE OF USE (% OF CLAIMANTS):	1.3%
NONADHERENCE (% OF CLAIMANTS):	44.9%
AVERAGE COST PER CLAIMANT:	$10,075
DRUG TYPE CLASSIFICATION BY CLAIMS:	42% Traditional / 58% Specialty
DRUG TYPE CLASSIFICATION BY SPEND:	5% Traditional / 95% Specialty

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	infliximab	Remicade® / Inflectra® / Renflexis™	Specialty	28.8%
2	adalimumab	Humira®	Specialty	25.9%
3	ustekinumab	Stelara®	Specialty	10.4%
4	etanercept	Enbrel® / Brenzys® / Erelzi™	Specialty	7.9%
5	golimumab	Simponi®	Specialty	4.4%
	Others			22.6%

SPENDING RANK #2 – DIABETES

The diabetes therapy class had the highest level of spending among traditional therapies for the last three years. Overall spending (10.1%) and the percentage of claimants (7.7%) increased over 2017, when overall spending and the percentage of claimants were 9.4% and 7.5%, respectively.

Diabetes is a chronic condition that often results in severe complications if blood glucose levels are not controlled. About 11 million Canadians live with diabetes or prediabetes in 2019, and the costs of treating the disease have soared from $14 billion in 2008 to just under $30 billion in 2018.

Between 5% and 10% of people with diabetes have type 1, where the pancreas does not produce insulin. Type 2 diabetes occurs when the body can't properly use insulin that is released, does not make enough insulin, or a combination of these. This accounts for the other 90%. Hyperglycemia, or high levels of blood glucose, is a common effect of uncontrolled diabetes. Over time, high blood glucose levels damage many of the body's systems, including the heart, eyes, kidneys and nerves. About 30% of strokes, 40% of heart attacks, 50% of kidney failures requiring dialysis and 70% of non-traumatic lower-limb amputations are diabetes-related.

The diabetes therapy class includes medications, insulin and diabetic supplies such as blood glucose test strips, lancets and syringes. The breakdown of spending in this therapy class is as follows: medications (56.4%), insulin (21.5%) and supplies (22.1%).

The overall trend, 6.6%, was driven mainly by an increase in cost per prescription (5.3%). Utilization increased slightly, at 1.4%.

There are a number of drug classes that target different abnormalities associated with type 2 diabetes to lower glucose levels. According to clinical guidelines, metformin is the first choice for treatment because of its efficacy, safety and low cost. If metformin and lifestyle modifications are inadequate, other medications may be added.

Second-line glucose-lowering medications include dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors), glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists), sodium-glucose transport-2 inhibitors (SGLT2 inhibitors), insulin secretagogues, thiazolidinediones and insulin.

- **DPP-4 inhibitors** lower blood glucose by increasing insulin levels after meals and by lowering glucagon levels (a hormone that raises blood glucose). They are well tolerated and are associated with a low risk of hypoglycemia (dangerously low blood glucose levels). Typically, these drugs are added as second- or third-line treatments when blood glucose is not controlled with metformin. DPP-4 inhibitors include Trajenta® (linaliptin), Nesina® (alogliptin), Onglyza® (saxagliptin) and Januvia® (sitagliptin).
- **GLP-1 receptor agonists** are injectable medications that mimic the actions of GLP-1, a hormone produced by the body. GLP-1 increases insulin secretion, suppresses glucagon secretion after eating, slows digestion and increases satiety, resulting in better control of glucose levels. GLP-1 receptor agonists are associated with weight loss and a low risk of hypoglycemia. They include Victoza® (liraglutide), Byetta® / Bydureon® (exenatide), Trulicity® (dulaglutide) and Adlyxin™ (lixisenatide).
- **SGLT2 inhibitors** prevent glucose reabsorption in the kidneys, leading to increased excretion of urinary glucose, and lower blood glucose. They are associated with weight loss and a low risk of hypoglycemia. SGLT2 inhibitors include Invokana® (canagliflozin), Forxiga® (dapagliflozin) and Jardiance™ (empagliflozin).
- **Insulin secretagogues** help the pancreas release more insulin. Examples include Diamicron® (gliclazide) and GlucoNorm® (repaglinide).
- **Thiazolidinediones**, similar to metformin, make the body's tissues more sensitive to insulin. Side effects include weight gain and an increased risk of heart failure and fractures. Thiazolidinediones include Actos® (pioglitazone) and Avandia® (rosiglitazone).

- **Insulin therapy** may be needed as well. Often, patients with type 2 start with one injection of long-acting insulin at night, but a mixture of insulin types may be required.

Within the top five, branded medications Janumet®/ Janumet® XR (rank #2), Victoza® (rank #4) and Jardiance™ (rank #5) accounted for 27.2% of spending. Janumet is a combination product containing Januvia and metformin. As of 2018, metformin is no longer ranked in the top five.

As mentioned above, insulin accounts for 21.5% of spending in the diabetes therapy class. Of note:

- Basaglar™ (insulin glargine) launched in December 2015 – the first biosimilar insulin to Lantus® – helped reduce insulin spending. Lantus remained in rank #3 in 2018, yet spending decreased for insulin glargine to 9.5% (2018) from 10.3% (2017). Basaglar offers a 25% cost saving over Lantus. Biosimilar share of claims for Basaglar increased from 1.1% (2017) to 4.6% (2018).
- The second biosimilar in this class, Admelog® (insulin lispro), was approved in December 2017 but has not yet been launched. A rapid-acting insulin, Admelog is highly similar to the reference product Humalog®, with comparable quality, safety and efficacy.

Diabetes treatment continues to be a focus of drug development. Many of these new drugs have higher costs compared to existing therapies.

- In February 2018, the sixth GLP-1 agonist, Ozempic® (semiglutide), was approved. Ozempic's full role in therapy will evolve as additional information becomes available in the future about its role in cardiovascular risk reduction.
- Xultophy®, approved in April 2018, is the first fixed-ratio combination basal insulin / GLP-1 receptor agonist to become available. It can be used as an add-on therapy for people who are being treated with either a basal insulin or a GLP-1 receptor agonist and are unable to get to their glycemic targets. The single injection provides additional convenience and potentially improved adherence, compared to the administration of each drug separately. Soliqua™, approved in July 2018, is the second fixed-ratio combination basal insulin / GLP-1 receptor agonist to become available. Soliqua is intended to replace basal insulin therapy when basal insulin monotherapy or basal insulin in combination with oral antidiabetic drugs are not sufficient. Soliqua must be taken with meals, a consideration when comparing Soliqua with Xultophy.
- Approved in May 2018, Steglatro™ (ertugliflozin) is the fourth SGLT2 inhibitor approved in Canada for the treatment of type 2 diabetes. At present, there are no cardiovascular safety data available for Steglatro, with none expected until late 2019. Also approved, Steglujan™ is a fixed-dose combination of ertugliflozin and sitagliptin, a DPP-4 inhibitor, and Segluromet™ is a fixed-dose combination of ertugliflozin and metformin. Combining two drugs with different yet complementary modes of action has been shown to provide additive glycemic-lowering efficacy over either drug alone. The fixed-dose combination provides the added benefit of reducing the number of pills that patients must take, potentially improving adherence.
- Jardiance®, another SGLT2 inhibitor, received an additional indication approval in April 2018 to reduce the risk of cardiovascular death in patients who have diabetes and established cardiovascular disease.
- Invokana® received a new indication in January 2019 for prevention of major cardiovascular adverse events. Invokana was previously indicated as an adjunct to diet, exercise and standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes and established cardiovascular disease. Invokana is now more closely aligned with Jardiance in this respect and is the third drug in the diabetes class approved for reducing the risk of cardiovascular events.

Other clinical developments in diabetes include:

- The CARMELINA cardiovascular outcomes trial examined the impact of Trajenta® (linagliptin) against placebo on top of standard of care on cardiovascular (CV) and renal outcomes. The findings showed that Trajenta® demonstrated similar CV safety versus the placebo in adults with type 2 diabetes and high CV risk. Additionally, it demonstrated that Trajenta has the most established safety profile within the DPP-4 inhibitor drug class.
- The American College of Cardiology (ACC) and the American Heart Association released, in March 2019, updated guidelines that recommend the use of diabetes medications (SGLT2 inhibitors and GLP-1 receptor agonists) for primary prevention of cardiovascular disease; although after initial use of metformin has been attempted. This use is presently beyond current regulatory approvals for these drugs. This could potentially increase utilization of these drugs.

The diabetes spending trend is expected to intensify in the years ahead, reflecting increasing drug prices and higher utilization as well as expanded use of expensive diabetes therapies with positive cardiovascular effects.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
2	Diabetes	10.1%	1.4%	5.3%	6.6%

PREVALENCE OF USE (% OF CLAIMANTS):	7.7%
NONADHERENCE (% OF CLAIMANTS):	45.0%*
AVERAGE COST PER CLAIMANT:	$1,121
DRUG TYPE CLASSIFICATION BY CLAIMS:	100% Traditional
DRUG TYPE CLASSIFICATION BY SPEND:	100% Traditional

*Excludes diabetic supplies

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	blood glucose test strips	Contour® Next/ One Touch Verio®/ Others	Traditional	14.5%
2	sitagliptin-metformin	Janumet®/ Janumet® XR	Traditional	12.7%
3	insulin glargine	Lantus®/ Basaglar™/Toujeo™	Traditional	9.5%
4	liraglutide	Victoza®	Traditional	8.3%
5	empagliflozin	Jardiance®	Traditional	6.2%
	Others			48.8%

SPENDING RANK #3 – DEPRESSION

Depression is a severe, chronic, disabling disease that affects almost four million Canadians. It is the leading cause of disability worldwide. Severe depression is linked with death by suicide, the ninth-leading cause of death in Canada.

This therapy class ranked third in both prescription volume and overall spending, while its overall trend remained relatively flat (0.6%), primarily driven by a reduction in cost per prescription while utilization increased by 4.3% in 2018.

The top five drugs by market share captured 60.5% of spending within this class. All five drugs are available as generics, with the exception of Trintellix® (vortioxetine) and Pristiq® (desvenlafaxine). Trintellix, a novel serotonergic antidepressant, appeared in the top five for the first time in 2018. Although the first generic for Pristiq® was previously approved, it has yet to be launched to impact spending.

No new drugs targeting widespread, common depression are in the pipeline; pipeline development is focused on small populations who have severe, treatment-resistant depression. Looking ahead, cost per prescription reduction is likely to lessen due to generic saturation; utilization will continue to align with the annual incidence of new depression diagnoses. Some potential specialty products may impact the trend slightly, starting in 2019. All factors combined, we should expect a relatively flat trend for depression medications.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
3	Depression	5.2%	4.3%	-5.0%	-0.6%

PREVALENCE OF USE (% OF CLAIMANTS):	14.8%
NONADHERENCE (% OF CLAIMANTS):	36.9%
AVERAGE COST PER CLAIMANT:	$300
DRUG TYPE CLASSIFICATION BY CLAIMS:	100% Traditional
DRUG TYPE CLASSIFICATION BY SPEND:	100% Traditional

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	escitalopram	Cipralex®	Traditional	18.9%
2	desvenlafaxine	Pristiq®	Traditional	11.7%
3	duloxetine	Cymbalta®	Traditional	11.6%
4	venlafaxine	Effexor® XR	Traditional	9.6%
5	vortioxetine	Trintellix®	Traditional	8.7%
	Others	Others		39.5%

SPENDING RANK #4 – ASTHMA AND COPD

Asthma and chronic obstructive pulmonary disease (COPD), conditions treated primarily with traditional medications, ranked fourth in spending in 2018, with a high prevalence of claimants (13.5%). This therapy class was ranked fifth in 2017. Claim volume for specialty drugs within this class is small but growing, with specialty spending increasing from 17% in 2017 to 21% in 2018, contributing to the increase in cost per prescription.

Although COPD and asthma are considered separate respiratory diseases, some of the symptoms are common to both and are treated with the same medications.

The second-ranked drug by spending is Xolair® (omalizumab), a specialty drug approved for severe allergic asthma that is not adequately controlled with other treatments. Percentage of spending for Xolair within this therapy class increased to 17.3% (2018) from 16.4% (2017).

New drug and indication approvals in this class include the following:

- A new specialty medication in this class, Fasenra™ (benralizumab), was approved in early 2018. An adjunct therapy, Fasenra will be used for maintenance treatment of adult patients who have severe eosinophilic asthma. Unlike the drugs to which it is compared, Nucala™ (mepolizumab) and Cinqair™ (reslizumab), its subcutaneous administration combined with an eight-week dosing schedule may represent a practical advantage. Utilization for Nucala and Cinqair is low; these two medications account for less than 5% of specialty spending within this class.
- Bevespi Aerosphere® (glycopyrronium/formoterol fumarate dihydrate), approved in March 2018, is a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting beta2-agonist (LABA), indicated for the long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. Currently, Bevespi Aerosphere® is a therapeutic alternative to the other inhaled LAMAs and LABAs (both combination and single-entity products) for the management of COPD.
- Arbesda RespiClick®, approved in April 2018, contains the same active ingredients as Advair® (available as a metered-dose inhaler [MDI] and diskus), but is not interchangeable. Arbesda RespiClick potentially may be easier to use than the MDI, yet the concept is similar to the diskus product. As Arbesda RespiClick® does not seem to provide any therapeutic advantage over Advair and is not interchangeable, its place in therapy remains uncertain.
- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol), approved in May 2018, is a combination of an inhaled corticosteroid (ICS), long-acting muscarinic antagonist and a long-acting beta2-adrenergic agonist, indicated for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and emphysema, in patients who are not adequately treated by a combination of an ICS/LABA. It is not indicated for the relief of acute bronchospasm or asthma. It is the only fixed-dose triple therapy available in a single device with once-daily dosing.
- Nucala™ (mepolizumab, for injection) received a new indication in July 2018. Nucala is now indicated as an add-on to corticosteroids for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). Nucala provides longer duration of remission compared to placebo and leads to more remissions; however, only half of the patients treated experienced remission. Nucala is a potential alternative to older immunosuppressive agents that have higher risks of adverse effects.

The spending trend in this class is projected to decline with the possible approval of generics of Flovent® (fluticasone) and Advair® (fluticasone/salmetrol) in the coming years. Other new drugs may increase competition within the asthma therapy class, potentially decreasing costs in 2019 and beyond. The patent is expiring on Xolair® in the next few years, but no biosimilars are currently expected.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
4	Asthma and COPD	5.0%	-5.8%	6.6%	0.7%

PREVALENCE OF USE (% OF CLAIMANTS):	13.5%
NONADHERENCE (% OF CLAIMANTS):	71.7%*
AVERAGE COST PER CLAIMANT:	$309
DRUG TYPE CLASSIFICATION BY CLAIMS:	99% Traditional / 1% Specialty
DRUG TYPE CLASSIFICATION BY SPEND:	79% Traditional / 21% Specialty

*Excludes rescue inhalers (e.g. Ventolin®)

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	budesonide-formoterol	Symbicort®	Traditional	18.1%
2	omalizumab	Xolair®	Specialty	17.3%
3	fluticasone-salmeterol	Advair®	Traditional	14.1%
4	fluticasone	Flovent®	Traditional	9.4%
5	montelukast	Singulair®	Traditional	7.6%
	Others			33.5%

SPENDING RANK #5 – HIGH BLOOD PRESSURE

High blood pressure is the number one risk factor for stroke and a major risk factor for heart disease. It occurs when the pressure in the arteries is elevated, forcing the heart to work harder to pump blood through the body's blood vessels.

In 2018, the high blood pressure therapy class dropped to rank #5 in overall spending from rank #3 in 2017 due to a large reduction in cost per prescription. This therapy class composed of traditional drugs ranked first in claims volume, as observed in 2017. This class once again ranked highest in prevalence of claimants (17.4%) among the top ten therapy classes.

The overall trend decreased by 17.7%, the largest decline among the top ten therapy classes, primarily due to a 14.9% reduction in the cost per prescription. The average cost per claimant also decreased, to $246 (2018) from $279 (2017).

The first generic for Coversyl® (perindopril) and Coversyl® Plus (perindopril/indapamide) was approved in March 2018. Although Coversyl maintained its #1 ranking in 2018, Coversyl® Plus dropped to #4 from #3, likely due to the availability of its generic. Spending on perindopril and perindopril/indapamide declined to 18.7% in 2018 from 23.6% in 2017, also due to the availability of lower-cost generic alternatives. Greater impact should occur in 2019.

The first-time generic for Twynsta® (telmisartan/amlodipine), approved in 2018, is expected to have a negligible impact due to Twynsta's small market share, 1.2% of overall spending.

The negative trend in this class is expected to continue. Market saturation and dominance of generic medications will result in flat utilization and falling unit prices. The decline is likely to level off slightly in 2019 and 2020, as no new generics are expected.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
5	High Blood Pressure	4.8%	-2.8%	-14.9%	-17.7%

PREVALENCE OF USE (% OF CLAIMANTS):	17.4%
NONADHERENCE (% OF CLAIMANTS):	29.3%
AVERAGE COST PER CLAIMANT:	$246
DRUG TYPE CLASSIFICATION BY CLAIMS:	100% Traditional
DRUG TYPE CLASSIFICATION BY SPEND:	100% Traditional

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	perindopril	Coversyl®	Traditional	13.4%
2	amlodipine	Norvasc®	Traditional	11.1%
3	nifedipine	Adalat®	Traditional	6.0%
4	perindopril-indapamide	Coversyl® Plus	Traditional	5.3%
5	ramipril	Altace®	Traditional	4.4%
	Others			59.8%

SPENDING RANK #6 – CANCER

Nearly half of Canadians are expected to be diagnosed with cancer at some point during their lifetime. Although an increasing number of patients are surviving at least five years past their diagnosis, cancer continues to be the leading cause of death in Canada. About one in four Canadians are expected to die from the disease. This alarming reality means that the most prolific drug development underway is focused on cancer treatment.

Cancer ranked #6 by overall spending in 2018, up from #7 in 2017, with the highest spending trend among the top 10 classes. For 2018, the trend increased by 16.5% due to an 11.5% increase in cost per prescription (11.2% in 2017) and a 5% increase in utilization. Specialty spending accounts for 96% of the costs in this class.

The latest milestone in the treatment of cancer is gene therapy. The first gene therapy, Kymriah™ (tisagenlecleucel), was approved by Health Canada in September 2018 but has yet to become available for sale here. CAR-T therapy involves genetically altering an individual's T-cells with chimeric antigen receptors (CARs) that can find and destroy cancer cells that normal T-cells are not able to detect. Kymriah is approved to treat two kinds of cancer: acute lymphoblastic leukemia (ALL) in children and young adults; and diffuse large B-cell lymphoma, the most common type of non-Hodgkin lymphoma, in adults. The second gene therapy, Yescarta™(axicabtagene ciloleucel), was approved in February 2019 but is not yet available. Yescarta is indicated for relapsed or refractory large B-cell lymphoma. Both Kymriah and Yescarta are included in the Express Scripts Canada Hospital Drug Program. Kymriah and Yescarta are one-time treatments with estimated costs of between USD$373K and $475K. Based on how CAR-T cell therapy is used, it would be most suitable as a hospital-based therapy.

New developments continue. Below are some 2018 approval highlights; many of these new drugs contributed to the increase in cost per prescription:

- Imfinzi® (durvalumab)*: for the treatment of patients with urothelial carcinoma and for the treatment of non-small cell lung cancer.
- Lonsurf® (trifluridine and tipiracil): for the treatment of metastatic colorectal cancer.

- Bavencio™ (avelumab)*: for the treatment of metastatic Merkel cell carcinoma.
- Besponsa™ (inotuzumab ozogamicin): for the treatment of acute lymphoblastic leukemia.
- Erleada™ (apalutamide): for the treatment of prostate cancer.
- Alunbrig™ (brigatinib)*: for the treatment of non-small cell lung cancer.
- Cabometyx™ (cabozantinib): for the treatment of renal cell carcinoma.

*Approved by Health Canada with a notice of compliance with conditions (NOC/c).

Health Canada approved the first biosimilar in this class in 2018. MVASI™, a biosimilar for Avastin® (bevacizumab), was approved for metastatic colorectal cancer and locally advanced, metastatic or recurrent non-small cell lung cancer. Upcoming biosimilars expected for cancer treatment include trastuzumab and rituximab.

The spending trend in this class will continue to rise. The use of cancer medications as maintenance therapies will continue to steadily increase the utilization of expensive drugs. Additionally, the increasing use of self-administered therapies will result in higher utilization and cost as coverage is transferred from public plans (for drugs administered in hospital) to private plans and patients (for drugs administered outside hospitals). Cancer drugs approved in 2018 and many more of those currently waiting for approval will contribute to higher costs within this therapy class.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
6	Cancer	4.4%	5.0%	11.5%	16.5%

PREVALENCE OF USE (% OF CLAIMANTS):	1.5%
NONADHERENCE (% OF CLAIMANTS):	46.8%
AVERAGE COST PER CLAIMANT:	$2,449
DRUG TYPE CLASSIFICATION BY CLAIMS:	38% Traditional / 62% Specialty
DRUG TYPE CLASSIFICATION BY SPEND:	4% Traditional / 96% Specialty

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	lenalidomide	Revlimid®	Specialty	16.4%
2	leuprolide	Eligard®	Specialty	6.2%
3	ibrutinib	Imbruvica®	Specialty	5.8%
4	rituximab	Rituxan®	Specialty	5.1%
5	palbociclib	Ibrance®	Specialty	5.1%
	Others			61.4%

SPENDING RANK #7 – PAIN

Medications used to treat pain and inflammation include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and non-narcotic drugs. More than one in four plan members who made at least one prescription benefit claim in 2018 (27.8%) sought treatment for pain. This number decreased slightly from 28.2% in 2017, possibly due to the growing public concerns about opioid use.

One in eight claimants (12.5%) used opioid medications. Opioids are narcotics, such as morphine, codeine, and their derivatives, mainly used to relieve moderate to severe acute pain. For certain conditions, they are prescribed on a long-term basis (for example, for palliative care of cancer or severe chronic pain).

Almost half of all prescription claims (48.7%) within the pain therapy class are for opioids.

Multiple studies have shown an increased risk of new, persistent opioid use after an opioid prescription for acute pain, even among patients who undergo relatively minor low-pain surgery. Opioids should therefore be prescribed only when necessary, in the lowest effective dose and for the shortest duration necessary. The risk is dose-related – the higher the initial exposure (higher total dose, longer duration prescription), the greater the risk of long-term use, misuse and overdose. Current data shows that one in five people who are new to opioids when prescribed a 10-day supply will become long-term users.

Furthermore, claims analysis showed that nearly 60% of patients using opioids were taking them with other drugs that, when taken in combination with opioids, are dangerous and potentially fatal. These drugs include muscle relaxants and benzodiazepine anti-anxiety medications such as Xanax® (alprazolam) and Ativan® (lorazepam). Opioids, muscle relaxants and benzodiazepines all have sedating effects and can slow the respiratory system. Taking these medications together can increase these reactions exponentially.

While there are clinical circumstances when the combination of those drugs may be appropriate, these medication mixtures can have serious health consequences if not used with extreme caution. In fact, the combination of benzodiazepines and opioids is the most common cause of overdose deaths involving more than one drug.

Canada is the world's second highest per-capita consumer of opioids, after the United States, which has led to widespread misuse, dependence and addiction. In 2017, according to the latest data from the federal government, 11 Canadians died each day, on average, of opioid poisoning. Early interventions that include timely patient education on the risks, and limiting initial usage to the minimum required dosage and duration, are essential safety measures.

As a result of opioid concerns, the overall trend in this therapy class is expected to continue to decline. Spending for other pain medications and anti-inflammatory drugs may rise as physicians look for other ways to treat chronic and acute pain.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
7	Pain	3.8%	-1.6%	-4.9%	-6.5%

PREVALENCE OF USE (% OF CLAIMANTS):	27.8%
NONADHERENCE (% OF CLAIMANTS):	Not Applicable
AVERAGE COST PER CLAIMANT:	$115
DRUG TYPE CLASSIFICATION BY CLAIMS:	100% Traditional
DRUG TYPE CLASSIFICATION BY SPEND:	100% Traditional

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	oxycodone	Oxyneo®, Oxy-IR®	Traditional	10.5%
2	hydromorphone	Dilaudid®	Traditional	9.9%
3	esomeprazole-naproxen	Vimovo®	Traditional	9.2%
4	naproxen	Naprosyn®	Traditional	8.5%
5	tramadol-acetaminophen	Tramacet®	Traditional	8.4%
	Others			53.5%

SPENDING RANK #8 – INFECTIONS

This therapy class includes antibiotics, antifungals and antivirals.

- Antibiotics are indispensable in treating bacterial infections and controlling the spread of infectious bacterial diseases, saving millions of lives since their discovery.
- Antifungals are used to treat conditions such as athlete's foot and candidiasis as well as serious systemic infections such as cryptococcal meningitis.
- Antiviral drugs are used to treat specific viral infections such as shingles; wide-spectrum antivirals may be prescribed to treat various viral illnesses such as influenza.

Drugs used for high-cost infectious diseases, such as HIV/AIDS, chronic hepatitis C, and lung infections among cystic fibrosis patients, are in other, distinct therapy classes.

Drugs used to treat infections have a high utilization (40.4%) and rank fourth in terms of claims volume.

More conservative prescribing of antibiotics to minimize the emergence of resistance will continue to result in spending declines in this class.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
8	Infections	3.4%	-7.6%	-0.9%	-8.4%

PREVALENCE OF USE (% OF CLAIMANTS):	40.4%
NONADHERENCE (% OF CLAIMANTS):	Not Applicable
AVERAGE COST PER CLAIMANT:	$69
DRUG TYPE CLASSIFICATION BY CLAIMS:	99% Traditional / 1% Specialty
DRUG TYPE CLASSIFICATION BY SPEND:	92% Traditional / 8% Specialty

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	valacyclovir	Valtrex®	Traditional	13.9%
2	amoxicillin	Amoxil®	Traditional	10.5%
3	clarithromycin	Biaxin®	Traditional	6.2%
4	amoxicillin-clavulanic acid	Clavulin	Traditional	4.8%
5	azithromycin	Zithromax®	Traditional	4.4%
	Others			60.2%

SPENDING RANK #9 – MULTIPLE SCLEROSIS

An estimated one in 340 Canadians lives with multiple sclerosis (MS), which attacks the central nervous system, causing communication gaps between the brain and the rest of the body. Symptoms and disease progression vary widely – some patients lose the ability to walk while others experience long periods of remission.

This therapy class affected only 0.1% of claimants yet represented 3.2% of overall spending because of the high annual cost of treatment. The average cost per member increased to $19,693 in 2018, up from $19,251 in 2017. MS moved into the top 10 in 2018, from #12 in 2017 primarily due to a 7% increase in utilization.

This class is currently dominated by Gilenya® (fingolimod), Tecfidera® (dimethyl fumarate), Copaxone® (glatiramer acetate), Rebif®/Avonex® (interferon beta-1a) and Aubagio® (teriflunomide). These five drugs account for 79% of spending within this class.

In 2017, Health Canada approved Glatect™, the first alternative to Copaxone® (glatiramer acetate). It is priced at 70% of Copaxone and accounted for 1.3% of claims for the chemical ingredient glatiramer acetate in 2018.

2018 developments include:

- Zinbryta® (daclizumab), approved in 2017, was voluntarily withdrawn in 2018 due to reports of serious inflammatory brain disorders, including encephalitis.
- Ocrevus®(ocrelizumab) received a conditional indication (NOC/C) approval in 2018 for the management of adult patients with early primary progressive multiple sclerosis (PPMS) (as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity). It is the first drug approved for progressive MS. The indication is limited to early PPMS patients for whom the potential risks will be more acceptable, as they are expected to benefit the most.
- In November 2018, Gilenya® (fingolimod) was also approved for a new indication: monotherapy for the treatment of pediatric patients between 10 and 17 years of age with relapsing multiple sclerosis to reduce the frequency of clinical exacerbations. Although well studied in adults, few disease-modifying drugs for the treatment of multiple sclerosis (MS) have been systematically evaluated in children. There is evidence that Gilenya is more effective than interferon beta-1a for treating pediatric MS.

Most of the movement in this class is between existing branded therapies. Expect a slightly positive trend due to increases in both cost per prescription and utilization.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
9	Multiple Sclerosis	3.2%	7.0%	2.1%	9.1%

PREVALENCE OF USE (% OF CLAIMANTS):	0.1%
NONADHERENCE (% OF CLAIMANTS):	32.2%
AVERAGE COST PER CLAIMANT:	$19,693
DRUG TYPE CLASSIFICATION BY CLAIMS:	100% Specialty
DRUG TYPE CLASSIFICATION BY SPEND:	100% Specialty

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	fingolimod	Gilenya®	Specialty	20.5%
2	dimethyl fumarate	Tecfidera™	Specialty	16.9%
3	glatiramer acetate	Copaxone®	Specialty	15.2%
4	teriflunomide	Aubagio®	Specialty	14.8%
5	interferon beta-1a	Avonex® / Rebif®	Specialty	11.7%
	Others			20.9%

SPENDING RANK #10 – ULCER AND REFLUX

Drugs used to treat gastric ulcers and gastroesophageal reflux include proton-pump inhibitors (PPIs) and histamine H2 receptor antagonists (H2RAs).

The overall trend for this class decreased by 11.0% as a result of reductions in both cost per prescription (7.3%) and utilization (3.6%). This class is made up of traditional drugs, with PPIs accounting for the highest proportion of spending. Almost all PPIs in the top five are now available with marketed generics, with the exception of Dexilant® (dexlansoprazole) and Tecta® (pantoprazole magnesium).

This trend is projected to continue to decline due to deprescribing initiatives (the latest guidelines recommend deprescribing PPIs in adults who have completed four weeks or more of treatment for mild to moderate gastroesophageal reflux disease or esophagitis and whose symptoms are resolved) and because there are no new therapies in the pipeline for this class.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
10	Ulcer and Reflux	3.2%	-3.6%	-7.3%	-11.0%

PREVALENCE OF USE (% OF CLAIMANTS):	14.7%
NONADHERENCE (% OF CLAIMANTS):	46.4%
AVERAGE COST PER CLAIMANT:	$190
DRUG TYPE CLASSIFICATION BY CLAIMS:	100% Traditional
DRUG TYPE CLASSIFICATION BY SPEND:	100% Traditional

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	esomeprazole magnesium	Nexium®	Traditional	32.6%
2	dexlansoprazole	Dexilant®	Traditional	20.6%
3	pantoprazole sodium	Pantoloc®	Traditional	17.5%
4	lansoprazole	Prevacid®	Traditional	9.9%
5	pantoprazole magnesium	Tecta®	Traditional	5.3%
	Others			14.4%

OTHER NOTABLE THERAPY CLASSES – HIGH CHOLESTEROL

In 2018, a negative spending trend continued for medications used to treat high cholesterol (15.9%), moving this class out of the top 10. This decline is primarily due to a substantial decrease in cost per prescription (11.9%), as well as a reduction in utilization (4%). This was heavily impacted by the pan-Canadian Generic Value Price Initiative with the top three molecules by spend, rosuvastatin, atorvastatin and ezetimibe, dropping to 10% of the reference brand cost as of April 1, 2018.

Traditional medications make up 99% of market share by claims in this class and include statins, fibrates, cholesterol absorption inhibitors, bile-acid sequestrants and niacin (nicotinic acid) derivatives, all of which are available as generics.

Specialty drugs for high blood cholesterol, which include PCSK9 inhibitors, are included in this therapy class. PCSK9 inhibitor use continues to be low as a result of vigorous clinical prior authorization criteria resulting in a higher than average rejection rate.

Repatha® (evolocumab) ranked #4 in 2018, up from #6 in 2017 and #14 in 2016.

In June 2018, Repatha received a new indication. Repatha is now indicated as an adjunct to diet and standard of care to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adult patients with atherosclerotic cardiovascular disease. Patients who have met conventional LCL-C targets (e.g., <2.0mmol/L) and are at high risk of cardiovascular events may now gain additional risk reduction benefits with the addition of Repatha for further LDL-C lowering.

In August 2018, Repatha received another indication approval: as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated. This expansion in the approved indications for Repatha fills a gap in care for individuals who are statin intolerant and could potentially increase the utilization of this drug significantly.

Recent declines in spend driven by reduced cost per prescriptions may be countered in the future by increased utilization of PCSK9 inhibitor specialty drugs. This decline will be offset slightly by increased spending on specialty medications. Expect greater utilization of PCSK9 inhibitors and higher related spending.

2018 RANK	THERAPY CLASS	% OF OVERALL SPEND	TREND		
			UTILIZATION	COST	TOTAL
11	High Cholesterol	2.9%	-4.0%	-11.9%	-15.9%

PREVALENCE OF USE (% OF CLAIMANTS):	11.5%
NONADHERENCE (% OF CLAIMANTS):	22.9%
AVERAGE COST PER CLAIMANT:	$238
DRUG TYPE CLASSIFICATION BY CLAIMS:	99% Traditional / 1% Specialty
DRUG TYPE CLASSIFICATION BY SPEND:	91% Traditional / 9% Specialty

TOP DRUGS BY SPEND	DRUG NAME	COMMON (REFERENCE) BRAND	DRUG TYPE	% OF SPENDING WITHIN CATEGORY
1	rosuvastatin	Crestor®	Traditional	39.8%
2	atorvastatin	Lipitor®	Traditional	29.2%
3	ezetimibe	Ezetrol®	Traditional	6.6%
4	evolocumab	Repatha®	Specialty	5.6%
5	fenofibrate	Lipidil®	Traditional	3.6%
	Others			15.3%

NATIONAL AND PROVINCIAL OVERVIEW

NATIONAL AND PROVINCIAL OVERVIEW

- NOTEWORTHY NATIONAL DEVELOPMENTS
- PROVINCIAL OVERVIEW

NOTEWORTHY NATIONAL DEVELOPMENTS

UPDATE ON PATENTED MEDICINE PRICES REVIEW BOARD (PMPRB) REFORM

In 2017, the Government of Canada proposed changes that would modernize the framework of the Patented Medicine Regulations, reflecting the evolution of the pharma sector and making prescription drugs more affordable for Canadians.

The new guidelines are expected to take a risk-based approach to price regulation that considers value and affordability, in addition to list prices in comparable countries.

Within this framework, all new drugs will have a maximum list price (MLP) based on the median of the 12 comparator countries chosen. Drugs will be classified as Category 1 (first-in-class or providing a substantial improvement over existing therapies) or Category 2 (all other drugs). Pharmacoeconomics, market size and gross domestic product factors will be applied, depending on the classification, to determine the list price. The MLP will apply for three years or until the drug is sold in seven countries, when it will be "frozen". Only if a new treatment indication is approved, sales exceed market size, new evidence of cost-effectiveness is shown, or significant changes in international pricing occur will MLPs be re-evaluated.

The finalized guidelines are expected later in 2019. The PMPRB reform will provide more transparency in drug pricing in Canada and eventually lower costs. These changes will benefit public and private plans as well as Canadians who pay for all or part of their prescriptions out-of-pocket.

CANNABIS LEGALIZATION

The Cannabis Act, which provides a strict legal framework for controlling the production, distribution, sale and possession of cannabis across Canada, came into force in October 2018. Since then, Canadians 18 years of age or older may legally possess up to 30 grams of cannabis (dried or equivalent) and may buy dried or fresh cannabis from provincially licensed retailers. The sale of cannabis edibles and concentrates is expected to become legal later in 2019.

Retail models fall under provincial jurisdiction. Some provinces decided to adopt a public model (such as Quebec and all Atlantic provinces); others decided on a private model (Ontario, Manitoba, Saskatchewan, Alberta); British Columbia adopted a mixed model.

Although legalization of recreational cannabis does not affect the current regulations around medical cannabis, it appreciably raised public interest. Increased demand for medical cannabis is therefore likely, prompting questions regarding the type of coverage plan sponsors will provide. The indications for which medical cannabis has demonstrated efficacy are very narrow (pain management in palliative care, cancer and multiple sclerosis) and there are currently no guidelines in terms of dosing. There is therefore a pressing need to develop solutions that will optimize medical cannabis coverage and ensure it is used in accordance with the most comprehensive data available. Express Scripts Canada is working closely with its clients to develop these solutions.

NATIONAL PHARMACARE

Discussions are still underway in regard to the implementation of a National Pharmacare plan. The main goal is improving access to medications for Canadians who cannot afford them despite coverage by public and/or private plans. The Advisory Council on the Implementation of National Pharmacare issued an interim report in March 2019 that laid out the core principles and foundational elements for successful implementation.

Among those recommendations is the creation of a national drug agency that would manage the program and provide guidance and advice to governments. The agency would consolidate many of the prescription drug-related functions currently managed by various levels of government. The council also recommended the development of a comprehensive, evidence-based national formulary to harmonize coverage across the country. Special considerations would be given to treatment for rare diseases.

The question of which national pharmacare model will be recommended has not yet been addressed but is expected in the council's final report, along with the architecture and implementation plan.

Discussions include models focused on expensive drugs, including those for rare diseases; a "fill in the gaps" approach targeting the most vulnerable Canadians; and a single-payer public model with coverage ranging from essential medicines to a more comprehensive formulary. The many possible options would all have different consequences on patient outcomes, access to medicines, public and private cost and the budget required to implement. The final report from the Advisory Council is expected in June 2019. It will evaluate the different options in regard to the model and implementation of pharmacare throughout Canada.

National pharmacare is looking large in the 2019 Federal Budget. It focuses on three key issues supporting the initial interim recommendations from the Advisory Council:

- The creation of a Canadian Drug Agency with a mission to negotiate drug prices.
- The creation of a new National Drug Formulary, intended to provide additional consistency in drug coverage in the country.
- The creation of a National Strategy for Drugs for Rare Diseases, an investment of up to $1B over two years to help Canadians suffering from rare diseases to access the drugs they need through a national strategy for high-cost drugs.

With federal elections coming in October 2019, national pharmacare has officially become an election issue. As the anticipated impact on plan sponsors will be significant, Express Scripts Canada continues to monitor these developments closely.

USMCA

On September 30, 2018, the United States, Mexican and Canadian governments announced they had reached an agreement on the modernized United States-Mexico-Canada Agreement (USMCA), intended to replace the North American Free Trade Agreement (NAFTA) currently in force. The new agreement, which will come into effect after each country's ratification, will change data protection for biologic drugs in Canada. Currently, data protection protects innovative drugs, biologic and non-biologic, from generic competition for a period of eight years. With USMCA, Canada agreed to extend the term for biologic drugs data protection to ten years. This extension could potentially have a substantial impact on the cost of drugs here by delaying access to biosimilars and could result in additional spending for plan sponsors.

OPIOID CRISIS

The opioid crisis continues in Canada, with a reported 3,996 deaths related to opioid poisoning in 2017, as compared to 2,946 in 2016. While campaigns continue to raise awareness among the medical community as well as the public, Health Canada has proposed reclassification of the opioid painkiller tramadol as a Schedule I narcotic under the Controlled Drug and Substances Act. This would place new restrictions on how it is prescribed and dispensed as a way of reducing abuse and dependence.

The Government of Canada also removed the requirement that physicians obtain an exemption to prescribe or administer methadone, an opioid agonist treatment. This change, which came into effect in May 2018, is intended to increase access to opioid addiction treatment.

PAN-CANADIAN PHARMACEUTICAL ALLIANCE (PCPA)

The pan-Canadian Pharmaceutical Alliance, or pCPA, conducts joint provincial and territorial negotiations for generics, biosimilars and brand name drugs. All brand name drugs submitted for funding through the national review process – Common Drug Review (CDR) or the pan-Canadian Oncology Drug Review (pCODR) – are considered for negotiation through the pCPA.

One of the results of these negotiations was the generic price initiative implemented in April 2018, a five-year agreement in which generic versions of nearly 70 of the most commonly prescribed drugs are now priced at 10% or 18% of the equivalent brand-name product, representing a discount of up to 90%.

The pCPA negotiations continue with the goal of achieving greater drug value for patients and plan sponsors.

PROVINCIAL OVERVIEW

BRITISH COLUMBIA

Private Drug Trend

The overall drug trend for private plans in British Columbia was 3.3% for 2018, higher than the national average of 0.9%. Both the cost per prescription (1.8%) and utilization (1.5%) contributed to the overall increase.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Smoking cessation. Coverage of smoking cessation products was limited to a single continuous course of treatment, lasting up to 12 weeks, and using one eligible smoking product each calendar year. As of June 2018, limits to ensure compliance with coverage maximums were introduced. If a person has already received coverage for their 12-week course of treatment in a calendar year, PharmaNet will refuse PharmaCare payment of any additional smoking cessation product costs. This means that claims may be submitted for private coverage, especially for patients who require combination therapies or treatment lasting longer than 12 weeks.

Hepatitis C treatment coverage extension. In March 2018, British Columbia expanded the clinical eligibility criteria to provide coverage to more patients living with hepatitis C. Treatment is now covered regardless of the type (genotype) or severity of the disease (fibrosis stage, presence of decompensated cirrhosis). This may reduce private plan spending.

Biosimilars. Since August 2018, BC PharmaCare covers Basaglar™ (biosimilar to Lantus®) for all patients who have received Special Authorization coverage for insulin glargine. Lantus will no longer be covered for new patients starting insulin glargine, but coverage will be maintained for patients already taking Lantus.

ALBERTA

Private Drug Trend

In 2018, the cost per prescription increased by 0.5% and utilization by 0.8%, which resulted in an overall trend of 1.3% for the province. It remains relatively similar to the national average.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

There were no noteworthy legislative or pharmacy practice changes identified in 2018.

SASKATCHEWAN

Private Drug Trend

The cost per prescription increased by 0.7% and utilization was up 1% for 2018, for an overall trend of 1.7%.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Hepatitis C treatment coverage extension. As of April 2018, Exceptional Drug Status (EDS) criteria for existing hepatitis C drugs have been updated. Hepatitis C patients may now qualify for EDS regardless of the disease severity or prognosis factors, and a reduction in private plan claims is anticipated.

Minor Ailment Program. In November, the Drug Plan and Extended Benefits Branch (DPEBB) and the Pharmacy Association of Saskatchewan reached a one-year agreement that expands the Minor Ailment Program. The list of conditions for which pharmacists can prescribe drugs has been extended, with the addition of nine minor ailments and self-care conditions, including shingles and uncomplicated urinary tract infection in women. Smoking cessation has also been added to the program as of January 2019.

Pharmacists in the province are now remunerated for the administration of medroxyprogesterone (Depo-Provera® and generics) by injection to eligible Saskatchewan residents.

Finally, the dispensing fee increased from $11.40 to $11.60 as of November 2018.

MANITOBA

Private Drug Trend

The overall drug trend for private plans in Manitoba was 2% in 2018, with utilization up 1.2% and cost per prescription up 0.8%. The overall provincial trend is double the national trend.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Biologics Reimbursement Policy. Since August 2018, Manitoba Health, Seniors and Active Living implemented a Tiered Biologics Reimbursement Policy. Tiering is now applied to specific biologic products (e.g. biosimilars and reference biologics) and indications for patients who have not used biologics before and those who have used and been unresponsive to biologic therapy. Private plans may see claims from members prescribed treatment not covered by the Tiered Reimbursement Policy.

Wholesale upcharge. Manitoba adjusted its wholesale upcharge rate or "Pharmaceutical Distribution Rate" in October 2018. A wholesale upcharge is defined as any supplemental cost added by wholesale distributors for distribution, storage and handling costs of pharmaceutical products. A rate of 5% is now applied on all brand products (previously around 10%). An increase to 5% (from 0%) applies to pan-Canadian Pharmaceutical Alliance (pCPA) generics; designated high-cost drugs for reduced pharmaceutical distribution remain at 2%.

ONTARIO

Private Drug Trend

Ontario is the only province to have an overall trend decline in 2018 (-0.6%). This is mainly because of lower utilization (a negative trend of 3.1%) resulting from the introduction of OHIP+, which paid for the majority of prescriptions filled by Ontario residents under 25 years of age. Cost per prescription increased by 2.5%, partly because the utilization of specialty medications has increased. In addition, OHIP+ paid claims tended to have a lower than average cost per prescription.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

OHIP+ update. The new Ontario government is changing OHIP+ to focus on providing benefits to those who need them the most. Children and youth who do not have existing prescription drug private plan benefits and are not eligible for the Ontario Drug Benefit Program (ODB) through social assistance will continue to receive coverage through OHIP+ without co-payments or deductibles. Beginning in April 2019, children and youth 24 years of age and under covered by private insurance will have to bill those plans. Individuals or families who have significant out-of-pocket costs despite having private coverage may apply for additional financial support through the Trillium Drug Program.

QUEBEC

Private Drug Trend

The overall trend in Quebec was up by 2.3%, a combination of an increase in cost per prescription (1.3%) and utilization (1%). The average cost per claimant is significantly higher in Quebec than in the rest of Canada, $1,009 versus $826, the result of higher utilization of specialty drugs in Quebec.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Biosimilars. Neupogen® was delisted from the RAMQ formulary, replaced by the biosimilar Grastofil® for all patients starting treatment. Previously approved patients on the brand-name drug are still covered until March 26, 2019, after which they will have to apply for exceptional coverage through *Médicament d'exception* or *Patient d'exception*. Neupogen continues to be covered for specific indications related to blood disorders.

After being delisted from the RAMQ formulary for new starts for multiple indications, Remicade® was reintroduced following an overturn of the minister's decision by the Quebec Court of Appeal. Starting February 11, 2019, Remicade® is now covered for all indications (except ulcerative colitis) but reimbursed at an amount equivalent to the lower-cost alternative (Renflexis™). All patients who are using Remicade for the first time after February 11 are subject to out-of-pocket costs.

Finally, Glatect® (a biosimilar to Copaxone®) was added to the RAMQ formulary for all new patients.

Private plans that choose to apply similar rules for biosimilar reimbursement will also capture savings.

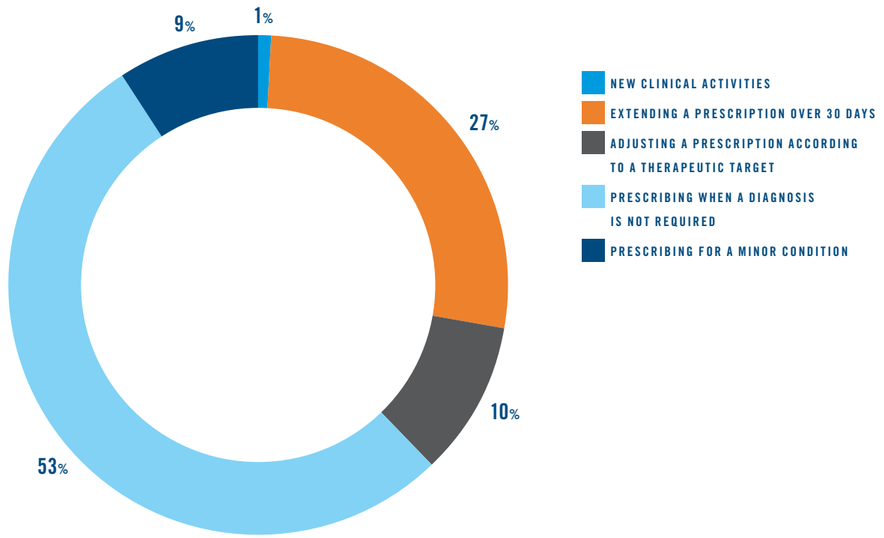
Expansion of Law 41 clinical activities. Since October 31, 2018, three clinical activities already authorized by Law 41 are now remunerated. Quebec pharmacists can now, for a fee:

- administer a drug for teaching purposes;
- substitute a drug in case of inventory issues; and
- adjust the dosage of a drug to ensure safety.

Two new clinical activities will also come into force as soon as modifications are made at the *Règlement sur le régime général d'assurance médicaments*. Pharmacists may then charge a fee for the management of patients in palliative care and posthospitalization.

Additionally, fees for all existing Law 41 clinical activities were increased at the same time and a subsequent increase is scheduled for April 2019.

DISTRIBUTION OF CLINICAL SERVICES CLAIMS FOR LAW 41 FOR 2018



There was an increase in the number of claims related to Law 41 clinical services in 2018. The number of claims increased by 10% from 2017, mostly attributable to the introduction of the new clinical services mentioned above and an increase in claims related to the adjustment of a prescription according to a therapeutic target. Other types of clinical services had a less drastic positive trend, with an increase in utilization and spending of around 5%.

The most popular service remains the prescription of a drug when a diagnosis is not required (as shown in the chart above) which includes smoking cessation, and malaria and traveller's diarrhea prevention.

This trend is predicted to persist for at least the next year, as these new services are used by more patients and others are introduced.

NEW BRUNSWICK

Private Drug Trend

The overall drug trend for private plans is 2%, largely driven by a 1.8% increase in cost per prescription. As the province of New Brunswick is a payer of last resort, private plans are directly impacted by spending growth.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

There were no noteworthy legislative or pharmacy practice changes identified in 2018.

PRINCE EDWARD ISLAND

Private Drug Trend

The overall trend for Prince Edward Island was 2.3%, with a cost per prescription growth of 1.7% and a utilization trend of 0.6%. PEI Pharmacare is a payer of last resort since 2014.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Biosimilars. Towards the end of 2018, Basaglar was added as an Open Benefit to PEI Pharmacare. Lantus, the brand reference drug, is still subject to approval through Special Authorization.

NOVA SCOTIA

Private Drug Trend

The overall trend for private plans in Nova Scotia was 1.3%, mainly driven by an increase of 1.2% in utilization and a stable cost per prescription (0.1%).

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Smoking cessation program. The Nova Scotia Pharmacare Program now provides coverage for the smoking cessation products vareclinine (Champix® and generic brands) and bupropion (Zyban®). Beneficiaries will be eligible for one course of 12 weeks (168 tablets) for either therapy each year without a special authorization approval. Additional reimbursement will be available through a special authorization request, provided that the patient fulfills certain criteria regarding readiness to quit, success with previous therapy and other relevant factors. As Nova Scotia is the payer of last resort, this measure is not expected to affect private plan spending.

Hepatitis C treatment coverage expansion. Since May 2018, Daklinza™, Epclusa®, Zepatier®, Harvoni® and Sovaldi® are considered for coverage regardless of the severity of the patient's condition (or fibrosis stage). Vosevi® was added to that list later in 2018. This has little impact on private plans as Nova Scotia is a payer of last resort.

NEWFOUNDLAND & LABRADOR

Private Drug Trend

The overall trend for private plans was up 1.1%, driven equally by increases in cost per prescription (0.6%) and utilization (0.5%). Spending growth in Newfoundland followed the overall national trend.

Noteworthy Developments Within the Provincial Public Drug Benefit Program

Biosimilars. Following the example of other provinces, Erelzi™ and Brenzys® (biosimilars to Enbrel®) were added to the Special Authorization Benefit list for specific indications for all newly diagnosed patients. Renflexis™ (biosimilar to Remicade®) was also added to the same list, for new patients requiring the drug. Finally, Basaglar, a Lantus biosimilar, was added to the Newfoundland and Labrador Prescription Drug Program (NLPDP).

"The Government of Canada proposed changes that would modernize the framework of the Patented Medicine Regulations, reflecting the evolution of the pharma sector and making prescription drugs more affordable for Canadians."

THE PHARMACY

LANDSCAPE

THE PHARMACY LANDSCAPE

- UPDATE ON PATENT EXPIRATIONS
- 2018 BIOSIMILARS INTRODUCTION
- A LOOK FORWARD
- PIPELINE

MARKET FORCES

UPDATE ON PATENT EXPIRATIONS

FIRST-TIME GENERICS

The introduction of new generic drugs contributes to lower overall drug costs.

In 2018, the generic versions of 16 brand name drugs were introduced to the Canadian market. These brand name therapies made up 1.62% of 2018 private plan spending, considerably less than the percentage of spending associated with brand name drugs for which generics became available in 2017.

The generics that became available in 2018 were mostly for traditional drugs. As interchangeability is not often a clinical issue within this drug category, potential savings are available to plan sponsors who adopt mandatory substitution plans.

Of note: generic versions became available for Coversyl®, a drug widely used to lower blood pressure, and Pradaxa®, a drug commonly prescribed to treat cardiovascular diseases.

A minimal number of patents for specialty drugs expired in 2018. These drugs do not represent a significant portion of overall spending, as detailed in the table below.

BRAND NAME DRUGS FOR WHICH GENERIC ALTERNATIVES WERE MADE AVAILABLE IN 2018

CATEGORY	BRAND NAME DRUG	CHEMICAL NAME	COMMON INDICATION	% OF TOTAL SPEND IN 2018
TRADITIONAL	Ofirmev®	Acetaminophen injection	Pain/Inflammation	n/a
	Toctino®	Alitretinoin	Skin Conditions	0.06%
	Volibris®	Ambrisetan	Pulmonary Hypertension	0.02%
	Abilify®	Aripiprazole	Mental Disorders	0.40%
	Entocort®	Budesonide	Steroids Anti-Inflammatory	0.04%
	Clobex Spray®	Clobetasol	Skin Conditions	0.04%
	Pradaxa®	Dabigatran	Cardiovascular Disease	0.12%
	Aggrenox®	Dipyridamole/ acetylsalicylic acid	Cardiovascular Disease	0.01%
	Monurol®	Fosfomycin tromethamine	Infections	0.03%
	Vimpat®	Lacosamide	Neurological Disorders	0.08%
	HpPAC®	Lansoprazole/amoxicilline/clarithromycine	Ulcer/Reflux	0.03%
	Bactroban Cream®	Mupirocin	Skin Conditions	0.00%
	Coversyl®	Perindopril	Infections	0.00%
	Coversyl Plus®	Perindopril/indapamide	High Blood Pressure	0.71%
	Twynsta®	Telmisartan/amlodipine beslate	High Blood Pressure	0.06%
	Aristopan®	Triamcinolone hexacetonide injection	Steroids Anti-Inflammatory	0.00%
	Levitra®	Vardenafil	Erectile dysfunction	0.02%
SPECIALTY	3-TC™	Lamivudine oral liquid	HIV/AIDS	0.00%
	Mepron®	Atovaquone	Infections	0.01%
	Vistide®	Cidofovir	Infections	n/a

2018 BIOSIMILARS INTRODUCTION

Health Canada approved a few biosimilars – drugs that are similar to the (often costly) brand reference biologic – in 2018.

As a biologic drug is made within a living cell and not from a chemical substance, the therapy molecule has natural variability and is often complex and larger than chemical drug molecules. It is therefore impossible to produce an identical biologic drug. To be approved, biosimilars are compared thoroughly to their brand name reference and must demonstrate high therapeutic similarity.

Because they are not identical, biosimilars and their reference drugs are not considered interchangeable, unlike non-biologic drugs and their generics. As interchangeability is not a practice that is necessarily endorsed by doctors in Canada, the use of biosimilars as a substitute for the reference drug is limited. For the most part, only newly diagnosed patients can start treatment with biosimilars. Health Canada recommends that a decision to switch a patient being treated with a reference biologic drug to a biosimilar should be made by the physician, in consultation with the patient, taking available clinical evidence and any policies of the relevant jurisdiction into account.

Despite not being interchangeable with brand reference drugs, the use of biosimilars is growing. First, as clinical experience with these products increases, physicians are more inclined to prescribe them. Additionally, many provinces have adopted policies that encourage mandatory use of biosimilars for newly diagnosed patients. For example, in Ontario, all newly diagnosed patients prescribed the drug Filgrastim must use the biosimilar Grastofil, funded under the Ontario Benefit Drug Program. Neupogen, Grastofil's reference biologic, is funded only under specific circumstances as a controlled benefit through the Exceptional Access Program. Private sponsors who decide to adopt similar policies will see increasing use of biosimilars and, consequently, lower spending.

Health Canada approved three biosimilars in 2018, but none of them were yet commercially available when this report was published.

The Humira® biosimilar, Hadlima™, is especially interesting. Humira® is a biologic drug widely used for various autoimmune diseases, including plaque psoriasis, Crohn's disease and rheumatoid arthritis. Biosimilars are often approved for fewer indications than their brand reference drug; Hadlima was approved for all but one of Humira's indications. Once Hadlima enters the market, we predict that its utilization will grow accordingly, leading to significant savings. Humira represented 3.76% of overall private plan spending in 2018.

Health Canada also approved the first biosimilar for the treatment of cancer in 2018. In the next few years, we expect to see many other biosimilars for oncology introduced to the Canadian market.

In addition, multiple competitors will launch their biosimilars for the same reference brand drugs, with different indications approved, leading to a more competitive pricing environment and further savings.

CHEMICAL NAME	BIOSIMILAR NAME	REFERENCE BRAND NAME BIOLOGIC	COMMON INDICATION	% OF TOTAL SPEND IN 2018
Adalimumab	Hadlima™	Humira®	Inflammatory Conditions	3.76%
Bevacizumab	Mvasi®	Avastin®	Cancer	0.05%
Pegfilgrastim	Lapelga® Fulphila®	Neulasta®	Blood Disorders	0.37%

A LOOK FORWARD

KEY PATENT EXPIRATIONS

In the next three to five years, patents will expire for multiple brands of both traditional and specialty drugs. This will lead to competition from generic drugs that is likely to translate into significant savings for private payers, especially those with mandatory substitution plans. (In many cases, generic prices are 10% to 25% of the equivalent brand name drug.)

Many highly utilized therapies for diabetes, multiple sclerosis, inflammatory conditions and cancer, among others, will have one or more generic versions entering the market by 2023.

The patents for Januvia®, Forxiga® and Onglyza®, three traditional antidiabetics, will expire between 2020 and 2022. Altogether, these brands made up 0.35% of total spending in 2018.

Highly utilized specialty drugs will also be subject to upcoming patent expirations, including Aubagio®, an oral drug used for multiple sclerosis. A generic could become available in 2022 when Aubagio's patent expires. Currently, Aubagio represents approximatively 0.48% of overall spending.

Patents will expire for multiple cancer drugs as well. There may be a generic version of Revlimid® on the market in the next five years. Revlimid is an oral cancer drug used to treat multiple myeloma, a rare type of cancer affecting about four in 100,000 people in Western industrialized countries. Even though utilization is low, Revlimid's cost is very high, estimated at $150,000 per year.

While this scenario is promising, it is important to note that litigation around patent expirations may delay the availability of some generics, also delaying potential savings.

Multiple biologic drug patents will expire in the next five years; consequently, more biosimilars will enter the market. Approval of a rituximab biosimilar is expected sometime between 2019 and 2021. Rituximab is prescribed for the treatment of certain types of blood cancer and autoimmune diseases such as rheumatoid arthritis. If the biosimilar gains approval for many of the indications approved for rituximab, its market penetration will increase, leading to meaningful savings for private plans.

The uptake of biosimilars will depend on many factors:

- The acceptance of interchangeability;
- The number of indications approved for the biosimilar as compared to the brand reference drug;
- The adoption of policies that favour the reimbursement of biosimilars;
- The number of competitors introducing biosimilars for each reference drug.

Again, issues around patent expirations might delay market entry of generics and biosimilars by a few years. Furthermore, in the new trade agreement between the United States, Canada and Mexico (USMCA), protection on biologic drugs has been extended from 8 to 10 years, shielding manufacturers from biosimilar competition for an additional two years. Altogether, these factors could increase upward pressure on costs.

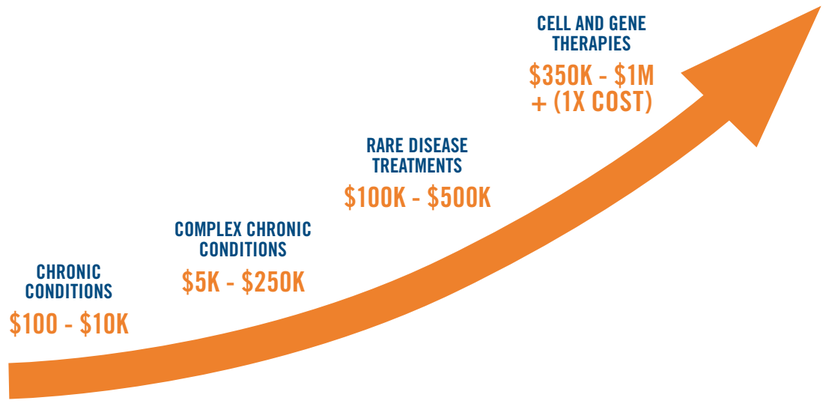
BIOSIMILARS UNDER DEVELOPMENT

CHEMICAL NAME	BRAND NAME REFERENCE DRUG	COMMON INDICATION	% OF OVERALL SPEND IN 2018	EXPECTED LAUNCH
Trastuzumab	Herceptin®	Cancer	0.00%	2019-2021
Rituximab	Rituxan®	Cancer	0.21%	2019-2021
Omalizumab	Xolair®	Asthma / COPD	0.84%	2019-2021
Ranibizumab	Lucentis®	Eye Diseases – Macular Degeneration	0.30%	2019-2021
Natalizumab	Tysabri®	Multiple Sclerosis	0.21%	2020-2022
Insulin aspart	NovoRapid®	Diabetes	0.30%	2022

UPDATE ON INNOVATIONS IN DRUG DEVELOPMENT IN 2018

PRESSURE ON SUSTAINABILITY OF THE DRUG BENEFIT

EVOLUTION OF DRUG DEVELOPMENT IN 2018



In the past year, pharmaceutical research and development has resulted in the introduction of breakthrough drugs that provide welcome hope to patients and their families. However, the high costs of these drugs also put considerable pressure on drug benefits sustainability. In general, pharmaceutical companies are now focused on specialty and niche drugs for which the price tag is very high, with more drugs in the development pipeline that, despite low utilization, mean enormous financial burdens for patients and payers. Drugs that treat rare diseases, for example, are often priced at hundreds of thousands of dollars per year. Those conditions are chronic and often require treatment for a lifetime. Cell and gene therapies are also contributing to the pressure on private plans.

NOTABLE DRUG INNOVATIONS IN 2018

We discussed, in last year's report, a potential new use for the drug Ilaris® (canakinumab). Originally, this high-cost drug was approved for the treatment of a family of rare inflammatory diseases. Ilaris® was also the object of a clinical trial for a new indication to reduce the risk of major cardiovascular events in patients with prior heart attack and atherosclerosis (CANTOS trial). Although promising in the beginning, results showed no statistical difference in mortality in patients using Ilaris® or a placebo. Consequently, the Food and Drug Administration has rejected the submission for cardiovascular diseases. However, benefits for patients with non-small cell lung cancer

were discovered during the trial and it prompted the start of clinical trials for Ilaris® as an oncology drug. Results should be available in 2022.

Gene therapies, including CAR-T cell therapies, remain a promising area of development in the pipeline. Although they generally target cancer, a potential new use for an inflammatory autoimmune condition called lupus is currently under investigation. Lupus is a chronic inflammatory disease that can virtually affect every organ. Symptoms can include pain, skin lesions, inflammation and failure of multiple organs like kidney and heart; the disease is characterized by periods of relapse and remission. While the cause of this disease is unknown, there is evidence that B cells play a central role in the course of the disease by producing autoantibodies in excess and activating other pathways of the immune system, which results in an intense inflammatory immune response. CAR-T cell therapy would allow to introduce modified T cell therapies in a patient that would target a specific protein that is found on B cells that produce autoantibodies. In mice, these modified T cells improved disease symptoms and progression. Although clinical trials are needed to ensure safety and efficacy of CAR-T cell therapies in humans, these preliminary results are promising and might widen the spectrum of diseases for which gene therapies can be effective. Approved CAR-T cell therapies are currently administered in a hospital setting; therefore, cost of these very expensive breakthrough drugs might not impact private payers.

DEVELOPMENT IN MIGRAINE THERAPY

Migraine is an often debilitating disease that is a major cause of disability and affects approximately 8.3% of Canadians.

Treatment often includes the long-term use of preventative drugs to reduce the number of episodes experienced.

In 2018, the first calcitonin gene-related peptide (CGRP) inhibitor was launched on the Canadian market. Aimovig™ constitutes a breakthrough, the first drug that directly targets a molecule implicated in the cascade of reactions that lead to a migraine attack. Aimovig is a biologic drug, administered subcutaneously, once a month, by the patient.

Although treatment is approved only for patients who experience at least four migraine days monthly, the prevalence of migraines makes the number of potential users very high. The annual cost for Aimovig ranges from $6,000 to $12,000, depending on the dosage. As more patients gain access to this specialty drug used for the treatment of a common condition, costs will increase substantially for private payers.

This field is expected to expand as other molecules targeting CGRP are in the pipeline, with one, galcanezumab, currently under review by Health Canada.

NEW ORPHAN DRUGS IN 2018

A rare disease is one that affects fewer than five in 10,000 persons in Canada. While the prevalence of these conditions is extremely low, there are currently over 7,000 rare diseases listed, cumulatively impacting about one in 12 Canadians.

Only a small number of treatments for these conditions are available, and none are curative. Rare diseases are complex conditions, often life-threatening, that have huge consequences on patients' health.

About 80% of rare diseases have a genetic component and are therefore more difficult to study. Low prevalence also limits research by restricting the number of eligible patients available for clinical trials. Consequently, prices for these therapies are ultra-high, putting significant pressure on private plans.

Two new drugs for rare diseases were commercialized in Canada in 2018, Radicava™ (edaravone) and Kanuma® (sebelipase alfa).

Radicava is indicated for amyotrophic lateral sclerosis or Lou Gehrig's disease (or ALS). ALS is a life-threatening, progressive disease that leads to general muscle weakness and, eventually, respiratory failure. There are currently 3,000 Canadians diagnosed with this disease. Radicava slows the progression of ALS in patients in the early disease stage, but this breakthrough comes at a high price – the annual cost is about $190,000 per year. Recently, the Institut national d'excellence en santé et services sociaux (INESS) in Quebec recommended that the RAMQ formulary include Radicava under the condition that

it be listed as a Médicament d'exception and that the manufacturer reduces the price. This inclusion would mean that private plans in Quebec would also have to provide coverage for this costly drug.

Kanuma® is used for the treatment of children and adults diagnosed with lysosomal acid lipase (LAL) deficiency. This genetic condition is characterized by an abnormal accumulation of fat in cells throughout the body, especially in the liver, within the first weeks of life. This accumulation of lipids leads to several health problems, including enlarged liver and spleen, vomiting, diarrhea, and poor absorption of nutrients. The result is tissue scarring, leading to cirrhosis and multi-organ failure. Infants generally do not survive past their first birthday. The annual cost of Kanuma is estimated to be $445,000 for infants and $666,588 for children and adults.

Some types of cancers are also considered rare diseases. Cancer can affect multiple organs and have many subtypes, depending on which genes mutate. For the same type of cancer, it is possible that one mutation is widespread and others rare. As treatments become more and more specialized, new drugs tend to target extremely specific forms of cancers, attacking cells with a particular mutation.

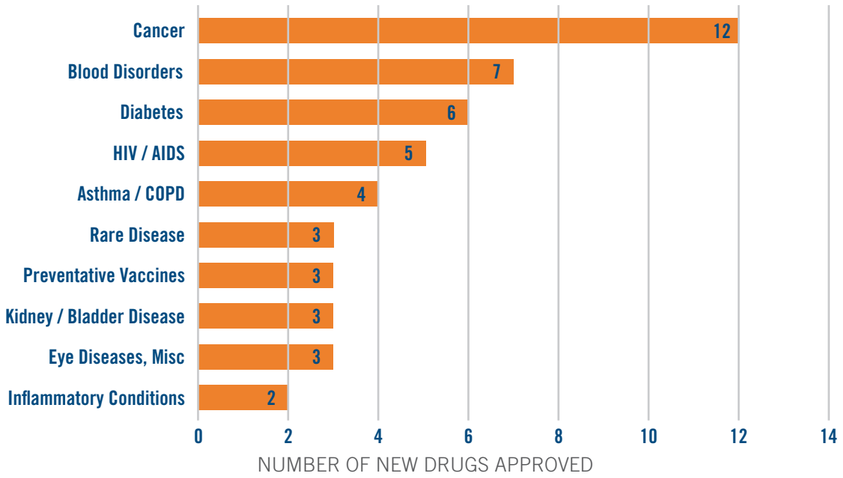
For example, in 2018, Rydapt™ (midostaurin) gained approval to treat mast cell leukemia, aggressive systemic mastocytosis and systemic mastocytosis with associated hematological neoplasm, three very rare forms of blood cancer. The annual cost of Rydapt for these indications is estimated at $483,000. Bavencio™ (avelumab), another drug approved in 2018, is approved for a rare type of skin cancer called Merkel cell carcinoma, which has a prevalence of 0.7 cases per 100,000 persons in the United States. The annual cost for Bavencio is estimated to be $137,000.

Although utilization may remain low for these indications individually, the collective cost of these and similar therapies will unquestionably put additional cost pressure on payers.

Continued medical innovation means that more rare cancers are diagnosed, and that novel treatments are developed with ever-increasing regularity. It is also predicted that the prevalence of these cancers may increase with the aging of the population.

NEW BRAND DRUG APPROVALS IN 2018

TOP 10 COMMON INDICATIONS FOR WHICH NEW DRUGS WERE APPROVED IN 2018



Newly approved drugs increased pressure on spending again in 2018, partly because a substantial portion was in the specialty category.

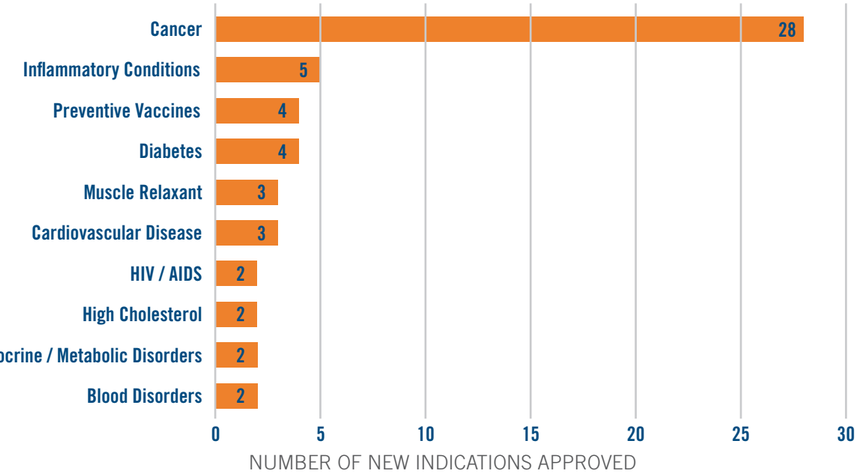
Cancer treatment once again leads in number of newly approved drugs, perpetuating a three-year trend. As most of these therapies are self-administered orally by the patient, private payers are more exposed to the enormous costs relative to these drugs. (Older oncology drugs were mainly administered in hospital and were therefore covered by public medical plans.)

See table *2018 New Brand Approvals* in Appendix.

NEW INDICATION APPROVALS IN 2018

See table *2018 New Indication Approvals* in Appendix

TOP 10 COMMON INDICATIONS FOR WHICH NEW INDICATIONS WERE APPROVED IN 2018



Approval of new indications for existing drugs continued to drive costs up, especially as more specialty drugs gained expanded use. For example, Repatha®, a drug that lowers cholesterol and costs about $7,000 per year of treatment, was approved for two additional indications in 2018: prevention of cardiovascular events and primary hyperlipidemia. As a consequence, the portion of overall spending for Repatha went from 0.01% in 2016 (a year after its initial approval) to 0.15% in 2018. Hypercholesterolemia is a widespread condition, so it is safe to assume that Repatha's impact on overall spending will continue to grow.

Cancer drugs have also gained their share of new indications this year, with 28 approvals. This is a slight increase over 2017 when 24 new indications were approved.

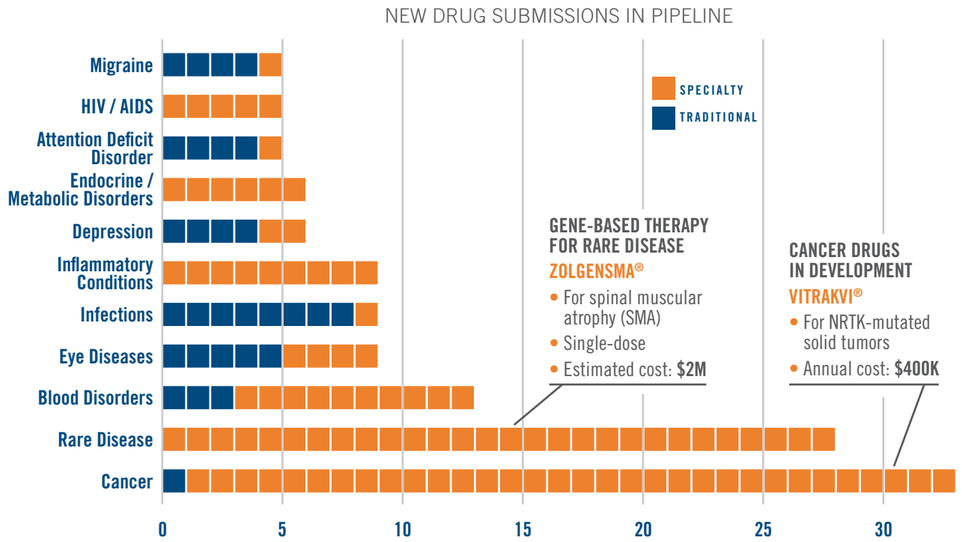
With more drugs designed for outpatient therapy (to be taken outside of the hospital setting), this trend is expected to continue for the foreseeable future.

PIPELINE

NEW MEDICATIONS IN THE DEVELOPMENT PIPELINE

DRUG DEVELOPMENT PIPELINE

NEW MEDICATIONS UNDER DEVELOPMENT



Unsurprisingly, based on recent trends, cancer therapies lead the drug development pipeline, with more than 30 drugs currently in Phase III clinical trials or under review by the FDA and/or Health Canada.

As mentioned, pharmaceutical companies are investing substantial resources in developing gene-based therapies and CAR-T cell therapies. Gene therapy is a technique that uses genes to treat or prevent diseases. Instead of using surgery or drugs, a gene is inserted into a patient's cells to:

- Replace a disease-causing mutated gene with a healthy gene;
- Inactivate a mutated gene that does not function properly;
- Introduce a new gene that will help fight a disease.

This technique is very promising for a number of diseases: genetic disorders currently without cures, some types of cancers and certain viral infections. In CAR-T cell therapy (chimeric antigen receptor T cells), the patient's T cells (a type of immune system cell) are modified in a laboratory to attack the patient's cancer cells. These 'upgraded' cells are then infused in large numbers into the patient's bloodstream. Currently, this technique is only used to treat some types of blood cancer.

The first gene-based therapy to be approved in Canada was Kymriah™ (tisagenlecleucel), in 2018. It is used to treat children and adolescents with resistant or recurring forms of acute lymphoblastic leukemia. As this drug requires administration in a hospital setting due to its complex monitoring requirements, it does not directly impact private plans. In early 2019, Yescarta® became the second

CAR-T cell therapy to be approved in the country. It is used to treat certain forms of blood cancers, non-Hodgkin and other large B-cell lymphomas.

Targeted oral therapies for cancer are also populating the pipeline. Vitrakvi® (laroctretinib), which has yet to be approved by Health Canada, is indicated for the treatment of solid tumours with a mutation of the NRTK fusion gene. This mutation is quite rare, with 2,500 to 3,000 new cases reported in the US each year. (Equivalent Canadian statistics are not available.) However, despite a predicted low utilization, its cost of almost $400K per year per patient could severely impact private plans.

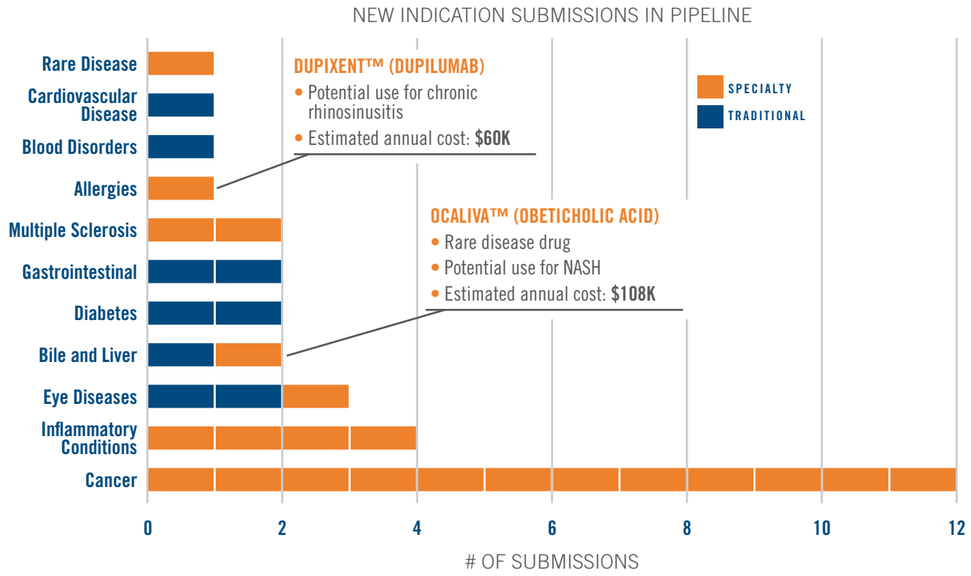
Treatments for rare diseases are also an important focus area in the pipeline. More than 25 drugs for these complex and life-threatening conditions are either in Phase III studies or under regulatory review. Gene-based therapies are also in development in this field.

Of note, the most expensive drug ever commercialized is scheduled for approval in 2019 in the United States. Zolgensma® (onasemnogene abeparvovec) is seeking approval for the treatment of spinal muscular atrophy Type 1. This drug would be administered just once, at the considerable price of USD$2M. The only drug currently approved for SMA is Spinraza™, which needs to be taken long-term, at the cost of $700K for the first year and around $350K in subsequent years. Zolgensma would be a direct competitor to Spinraza and, given the fact that the administration is likely to be in a hospital setting, its approval could potentially be beneficial for private payers that currently pay for Spinraza.

Refer to Appendix for a listing of possible near-term approvals of new brands.

EXPANSION OF USE OF HIGH-COST MEDICATIONS

DRUG DEVELOPMENT PIPELINE
EXPANDING INDICATIONS INCREASE UTILIZATION



Expansion of indications for already existing drugs will also add to cost pressures, especially as we are seeing more specialty drugs being used to treat common conditions.

Cancer is the drug category for which the largest number of existing medications are under review for use in other tumour types. As new indications are approved, utilization will increase along with spending.

The novel trend of using specialty medications to treat common conditions persists. Ocaliva™ (obeticholic acid) was initially approved in 2017 for the treatment of a rare disease called primary biliary cholangitis, which affects 19 to 402 cases per million. Its annual cost is estimated to be $38,000. There are currently Phase III studies underway to demonstrate the efficacy of Ocaliva for a more common indication, nonalcoholic steatohepatitis (or NASH), a liver disease that can lead to cirrhosis and cancer. NASH has a population prevalence of 2% to 5%, which makes it at least 50 times more prevalent than primary biliary cholangitis. The estimated annual cost for Ocaliva for the treatment of NASH is $108,000 per year, which could significantly increase costs for private payers. In the United States, the approval of Ocaliva for NASH is scheduled for 2019.

A new indication for Dupixent™ is also in the pipeline. Dupixent is given by injection, subcutaneously, to patients with atopic dermatitis when topical therapies have failed. It is currently being evaluated in a Phase III clinical trial for the treatment of chronic rhinosinusitis with nasal polyps. This common allergic condition used to be treated with corticosteroid nasal spray or elective surgery. Broadening Dupixent's indications to chronic rhinosinusitis will add to pressure on private plans, given the fact that its estimated annual cost is expected to be about $60K.

Refer to Appendix for a listing of possible near-term approvals of new indications currently under review by Health Canada.

> **"... pharmaceutical companies are investing substantial resources in developing gene-based therapies and CAR-T cell therapies. Gene therapy is a technique that uses genes to treat or prevent diseases."**

APPENDIX

- 2018 NEW BRAND APPROVALS
- 2018 NEW INDICATION APPROVALS
- DRUGS CURRENTLY UNDER REVIEW BY HEALTH CANADA FOR NEW BRAND APPROVALS
- DRUGS CURRENTLY UNDER REVIEW BY HEALTH CANADA FOR EXPANSION OF INDICATIONS

2018 NEW BRAND APPROVALS (IN ALPHABETICAL ORDER OF COMMON INDICATION)

CATEGORY	BRAND NAME	CHEMICAL NAME	COMMON INDICATION
TRADITIONAL	Emerade®	Epinephrine	Allergy
	Arbesda RespiClick™	Fluticasone propionate/ salmeterol	Asthma/COPD
	Bevespi Aerosphere®	Glycopyrronium/ formoterol fumarate	Asthma/COPD
	Trelegy Ellipta	Fluticasone furoate/ umeclidinium/ vilanterol	Asthma/COPD
	Foquest®	Methylphenidate hydrochloride	Attention Deficit Disorder
	Ozempic®	Semaglutide	Diabetes
	Steglatro™	Ertugliflozin	Diabetes
	Xultophy®	Insulin degludec/ liraglutide	Diabetes
	Steglujan™	Ertugliflozin/sitagliptin	Diabetes
	Segluromet™	Ertugliflozin/metformin	Diabetes
	Soliqua®	Insulin glargine/lixisenatide	Diabetes
	Invokamet XR®	Canagliflozin/metformin	Diabetes
	Bydureon BCise®	Exenatide LAR	Diabetes
	Orilissa®	Elagolix	Endocrine/Metabolic Disorders
	Restasis MultiDose™	Cyclosporine	Eye Diseases, Misc
	Xiidra®	Lifitigrast	Eye Diseases, Misc
	Xydalba™	Dalbavancin	Infections
	Stromectol®	Ivermectin	Infections
	Mezera™	Mesalazine	Inflammatory Bowel Disease
	Rayaldee®	Calcifediol	Kidney/Bladder Disease
	Veltassa®	Patiromer	Kidney/Bladder Disease
	Probuphine®	Buprenorphine	Pain/Inflammation
	Sublocade™	Buprenorphine	Pain/Inflammation
	Penthrox®	Methoxyflurane	Pain/Inflammation
	Afluria® Tetra	Quadrivalent influenza vaccine	Preventative Vaccines
	KamRAB™	Human rabies immunoglobulin	Preventative Vaccines
	Kuvan®	Sapropterin	Rare Disease
	Belsomra®	Suvorexant	Sedative/Hypnotic
	Eucrisa®	Crisaborole	Skin Conditions
	Fucibet®	Fusidic acid/ betamethasone	Skin Conditions
	Contrave®	Bupropion/naltrexone	Weight Loss
SPECIALTY	Fasenra™	Benralizumab	Asthma/COPD
	Alphanate®	Antihemophilic Factor/von Willebrand Factor Complex	Blood Disorders
	Rebinyn®	Nonacog beta pegol	Blood Disorders
	Monoferric™	Iron isomaltoside	Blood Disorders
	Panhematin®	Hemin	Blood Disorders
	Hemlibra®	Emicizumab	Blood Disorders
	Takhzyro™	Lanadelumab	Blood Disorders
	Jivi®	Damoctocog alfa pegol	Blood Disorders
	Alunbrig®	Brigatinib	Cancer
	Unituxin®	Dinutuximab	Cancer
	Lonsurf®	Trifluridine/tipiracil hcl	Cancer
	Bavencio™	Avelumab	Cancer
	Lartruvo™	Olaratumab	Cancer
	Imfinzi®	Durvalumab	Cancer
	Besponsa®	Inotuzumab ozogamicin	Cancer
	Erleada™	Apalutamide	Cancer
	Kisqali®	Ribociclib	Cancer
	Folotyn®	Pralatrexate	Cancer
	Cabometyx®	Cabozantinib	Cancer
	Herceptin® SC	Trastuzumab	Cancer
	Kymriah®	Tisagenlecleucel T	Cancer
	Lartruvo®	Olaratumab	Cancer
	Nuceiva™	Prabotulinumtoxina	Cosmetic Agents
	Symdeko®	Tezacaftor/ivacaftor + ivacaftor	Cystic Fibrosis
	Iluvien®	Fluocinolone acetonide	Eye Diseases, Misc
	Xermelo®	Telotristat ethyl	Gastrointestinal disease
	Pifeltro™	Doravirine	HIV/AIDS
	Symtuza™	Darunabir/cobicistat/ emtricitabine/ tenofovir alafenamide	HIV/AIDS
	Juluca®	Dolutegravir/rilpivirine	HIV/AIDS
	Biktarvy®	Bictegravir/ emtricitabine/ tenofovir alafenamide	HIV/AIDS
	Delstrigo™	Doravirine/lamivudine/tenofovir disoproxil fumarate	HIV/AIDS
	Pergoveris®	Follitropin alfa/lutropin alfa	Infertility
	Rekovelle®	Follitropin delta	Infertility
	Benlysta®	Belimumab	Inflammatory Conditions
	Kevzara®	Sarilumab	Inflammatory Conditions
	Actemra®	Tocilizumab	Inflammatory Conditions
	Siliq™	Broadalumab	Inflammatory Conditions
	Olumiant™	Baricitinib	Inflammatory Conditions
	Orencia®	Abatacept	Inflammatory Conditions
	Velphoro®	Sucroferric oxyhydroxide	Kidney/Bladder Disease
	Aimovig®	Erenumab	Migraine
	Addyi®	Flibanserine	Misc
	Tegsedi™	Inotersen	Neurological Disorders
	Cutaquig®	Immune globulin (human)	Preventative Vaccines
	Kanuma®	Sebelipase alfa	Rare Disease
	Radicava®	Edaravone	Rare Disease
	Crysvita®	Burosumab	Rare Disease

2018 NEW INDICATION APPROVALS (IN ALPHABETICAL ORDER OF COMMON INDICATION)

CATEGORY	BRAND NAME	CHEMICAL NAME	COMMON INDICATION
TRADITIONAL	Xarelto®	Rivaroxaban	Cardiovascular Disease
	Lovenox®	Enoxaparin sodium	Cardiovascular Disease
	Glyxambi®	Empagliflozin-linagliptin	Diabetes
	Bydureon®	Exenatide long-acting release	Diabetes
	Trajenta™	Linagliptin	Diabetes
	Invokana®	Canagliflozin	Diabetes
	Zaxine®	Rifaximin	Infections
	Abilify Maintena®	Aripiprazole	Mental Disorders
	Latuda®	Lurasidone	Mental Disorders
	Fycompa®	Perampanel	Neurological Disorders
	Aptiom®	Eslicarbazepine	Neurological Disorders
	Prolia®	Denosumab	Osteoporosis/Skeletal Disorder
	Nimenrix®	Quadrivalent meningococcal vaccine	Preventative Vaccines
	Ixiaro®	Japanese encephalitis vaccine	Preventative Vaccines
	Hizentra®	Human immunoglobulin	Preventative Vaccines
	Bexsero®	Meningococcal B vaccine	Preventative Vaccines

CATEGORY	BRAND NAME	CHEMICAL NAME	COMMON INDICATION
SPECIALTY	Nucala®	Mepolizumab	Asthma/COPD
	Soliris®	Eculizumab	Blood Disorders
	Adynovate®	Antihemophilic factor [recombinant], PEGylated	Blood Disorders
	Opdivo®	Nivolumab	Cancer
	Rituxan® SC	Rituximab	Cancer
	Imbruvica®	Ibrutinib	Cancer
	Gazyva®	Obinutuzumab	Cancer
	Bavencio™	Avelumab	Cancer
	Darzalex®	Daratumumab	Cancer
	Bosulif®	Bosulif	Cancer
	Yervoy®	Ipilimumab	Cancer
	Giotrif®	Afatinib	Cancer
	Tagrisso®	Osimertinib	Cancer
	Ibrance®	Palbociclib	Cancer
	Avastin®	Bevacizumab	Cancer
	Zykadia®	Ceritinib	Cancer
	Alecensaro™	Alectinib	Cancer
	Imfinzi®	Durvalumab	Cancer
	Tafinlar®	Dabrafenib	Cancer
	Lynparza®	Olaparib	Cancer
	Zytiga®	Abiraterone	Cancer
	Tecentriq®	Atezolizumab	Cancer
	Rydapt®	Midostaurin	Cancer
	Keytruda®	Pembrolizumab	Cancer
	Tasigna®	Nilotinib	Cancer
	Venclexta®	Venetoclax	Cancer
	Mekinist®	Trametinib	Cancer
	Perjeta®	Pertuzumab	Cancer
	Dysport® Aesthetic	AbobotulinumtoxinA	Cosmetic Agents
	Orkambi®	Lumacaftor/ ivacaftor	Cystic Fibrosis
	Somatuline® Autogel®	Lanreotide acetate	Endocrine/Metabolic Disorders
	Signifor® LAR	Pasreotide pamoate	Endocrine/Metabolic Disorders
	Xiaflex®	Collagenase Clostridium Histolyticum	Enzymes
	Lucentis®	Ranibizumab	Eye Diseases, Macular Degeneration
	Repatha®	Evolocumab	High Cholesterol
	Tivicay®	Dolutegravir	HIV/AIDS
	Genvoya®	Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide	HIV/AIDS
	Isentress®	Raltegravir sodium	HIV/AIDS
	Isentress® HD	Raltegravir sodium	HIV/AIDS
	Orencia®	Abatacept	Inflammatory Conditions
	Simponi® IV	Golimumab	Inflammatory Conditions
	Taltz®	Ixekizumab	Inflammatory Conditions
	Cimzia®	Certolizumab pegol	Inflammatory Conditions
	Xeljanz®	Tofacitinib	Inflammatory Conditions
	Humira®	Adalimumab	Inflammatory Conditions
	Ocrevus®	Ocrelizumab	Multiple Sclerosis
	Gilenya®	Fingolimod	Multiple Sclerosis
	Dysport® Therapeutic	AbobotulinumtoxinA	Muscle Relaxant
	Botox®	Onabotulinumtoxin A	Muscle Relaxant
	Xgeva®	Denosumab	Osteoporosis/Skeletal Disorder

DRUGS CURRENTLY UNDER REVIEW BY HEALTH CANADA FOR NEW BRAND APPROVALS (IN ALPHABETICAL ORDER OF COMMON INDICATION)

CATEGORY	CHEMICAL NAME	COMMON INDICATION
TRADITIONAL	Trifarotene	Acne
	Prasterone	Alternative Medicine
	Bisoprolol fumarate	Cardiovascular Disease
	Hydrochlorothiazide, zofenopril calcium	Cardiovascular Disease
	Nicardipine hydrochloride	Cardiovascular Disease
	Zofenopril calcium	Cardiovascular Disease
	Mannitol	Cystic Fibrosis
	Glucagon	Diabetes
	Insulin glargine	Diabetes
	Sotagliflozin	Diabetes
	Dotatate	Diagnostic Agents
	Dexamethasone sodium phosphate, netilmicin sulfate	Eye Diseases
	Cinnarizine, dimenhydrinate	Gastrointestinal disease
	Plecanatide	Gastrointestinal disease
	Mesalazine	Gastrointestinal disease
	Tibolone	Hormone Replacement
	Fosfomycin sodium	Infections
	Sodium zirconium cyclosilicate	Kidney/Bladder Disease
	Naloxone hydrochloride dihydrate	Narcotic Antagonist
	Apomorphine hydrochloride	Neurological Disorders
	Levetiracetam	Neurological Disorders
	Magnesium chloride hexahydrate, potassium chloride, sodium acetate trihydrate, sodium citrate dihydrate, sodium phosphate dibasic, sodium phosphate monobasic, water	Nutritional Products
	Vitamin D3	Nutritional Products
	Romosozumab	Osteoporosis/Skeletal Disorder
	Bacillus Calmette-Guerin BCG	Preventative Vaccines
	Haemagglutinin-strain A(H1N1), haemagglutinin-strain A(H3N2), haemagglutinin-strain B(Victoria), haemagglutinin-strain B(Yamagata)	Preventative Vaccines
	Haemagglutinin-strain A(H1N1), haemagglutinin-strain A(H3N2), haemagglutinin-strain B(Victoria), haemagglutinin-strain B(Yamagata)	Preventative Vaccines
	Dermatophagoides farinae, dermatophagoides pteronyssinus	Skin Conditions
	Halobetasol propionate, tazarotene	Skin Conditions
	Hydrogen peroxide	Skin Conditions
	Mometasone furoate	Skin Conditions

CATEGORY	CHEMICAL NAME	COMMON INDICATION
SPECIALTY	Filgrastim (r-metHuG-CSF)	Blood Disorders
	Turoctocog alfa pegol	Blood Disorders
	Abemaciclib	Cancer
	Acalabrutinib	Cancer
	Belinostat	Cancer
	Bevacizumab	Cancer
	Cemiplimab	Cancer
	Larotrectinib	Cancer
	Neratinib maleate	Cancer
	Niraparib	Cancer
	Talazoparib	Cancer
	Trastuzumab	Cancer
	Esketamine hydrochloride	Depression
	Methylene blue	Diagnostic Agents
	Dolutegravir, lamivudine	HIV/AIDS
	Adalimumab	Inflammatory Conditions
	Darvadstrocel	Inflammatory Conditions
	Ravulizumab	Inflammatory Conditions
	Risankizumab	Inflammatory Conditions
	Rituximab	Inflammatory Conditions
	Galcanezumab	Migraine
	Teriparatide	Osteoporosis/Skeletal Disorder
	Ataluren	Rare Disease
	Patisiran	Rare Disease

DRUGS CURRENTLY UNDER REVIEW BY HEALTH CANADA FOR EXPANSION OF INDICATIONS (IN ALPHABETICAL ORDER OF COMMON INDICATION)

CATEGORY	CHEMICAL NAME	COMMON INDICATION
TRADITIONAL	Azelastine hydrochloride, fluticasone propionate	Allergy
	Budesonide, formoterol fumarate dihydrate	Asthma/COPD
	Umeclidinium bromide	Asthma/COPD
	Methylphenidate hydrochloride	Attention Deficit Disorder
	Emicizumab	Blood Disorders
	Dapagliflozin	Diabetes
	Empagliflozin	Diabetes
	Linagliptin	Diabetes
	Budesonide	Gastrointestinal disease
	Dexlansoprazole	Gastrointestinal disease
	Naloxegol oxalate	Gastrointestinal disease
	Palonosetron hydrochloride	Gastrointestinal disease
	Daptomycin	Infections
	Sevelamer carbonate	Kidney/Bladder Disease
	Hydromorphone hydrochloride	Pain/Inflammation
	Corynebacterium diphtheriae crm-197 protein, pneumococcal conjugate serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Preventative Vaccines
	Haemagglutinin-strain A(H1N1), haemagglutinin-strain A(H3N2), haemagglutinin-strain B(Yamagata)	Preventative Vaccines
	Pimecrolimus	Skin Conditions
SPECIALTY	Eltrombopag olamine	Blood Disorders
	Icatibant acetate	Blood Disorders
	Atezolizumab	Cancer
	Bevacizumab	Cancer
	Blinatumomab	Cancer
	Cabozantinib	Cancer
	Infliximab	Cancer
	Nivolumab	Cancer
	Olaparib	Cancer
	Palbociclib	Cancer
	Pembrolizumab	Cancer
	Pomalidomide	Cancer
	Regorafenib	Cancer
	Sunitinib malate	Cancer
	Levomilnacipran	Depression
	Glecaprevir, pibrentasvir	Hepatitis C
	Alirocumab	High Cholesterol
	Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide hemifumarate	HIV/AIDS
	Certolizumab pegol	Inflammatory Conditions
	Sarilumab	Inflammatory Conditions
	Secukinumab	Inflammatory Conditions
	Tocilizumab	Inflammatory Conditions
	Dimethyl fumarate	Multiple Sclerosis
	Teriflunomide	Multiple Sclerosis
	IncobotulinumtoxinA	Muscle Relaxant
	Macitentan	Pulmonary Hypertension
	Dupilumab	Skin Conditions

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LEAD AUTHOR

JOHN HERBERT, MBA
Director - Clinical, Research & New Solutions

CO-AUTHORS

AARON AOKI, RPh, BScPhm, MBA, CRE, CDE
Clinical Pharmacist

FARAH BELAYADI, PharmD
Clinical Pharmacist

SUZANNE EASO, RPh, BScPhm
Clinical Pharmacist

CONTRIBUTORS

STEVE KIM, BMath
Reporting Analyst

PETER MA, R.PhT
Clinical Services Associate

LEIGH-ANN MACPHERSON
Clinical Services Associate

RAMANJEET SINGH, BHS
Clinical Services Associate

RUI YAN, PhD
Data Scientist

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EXPRESS SCRIPTS CANADA

5770 Hurontario Street, 10th Floor
Mississauga, Ontario, L5R 3G5
Toll-free: 888-677-0111
Express-Scripts.ca

@ExpressRxCanada
Express Scripts Canada
Express Scripts Canada