

**A LOOK AT THE OVERALL DRUG TREND
FOR 2018**

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OVERALL TREND IN 2018

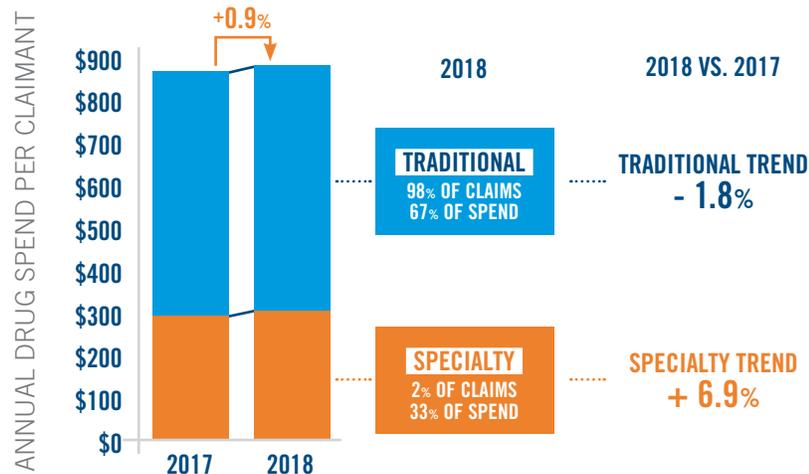
For plan sponsors, protecting plan sustainability starts with an understanding of the high-level influences that affect benefit spending and the health of members. In 2018, as for each year since the launch of our first annual Drug Trend Report, Express Scripts Canada leveraged the vast amount of data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

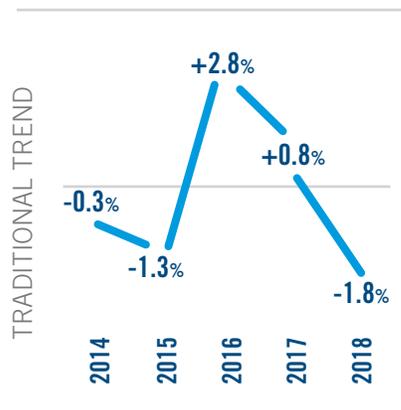
TRADITIONAL VS. SPECIALTY INCREASE IN SPECIALTY MASKED BY DECREASE IN TRADITIONAL



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



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



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

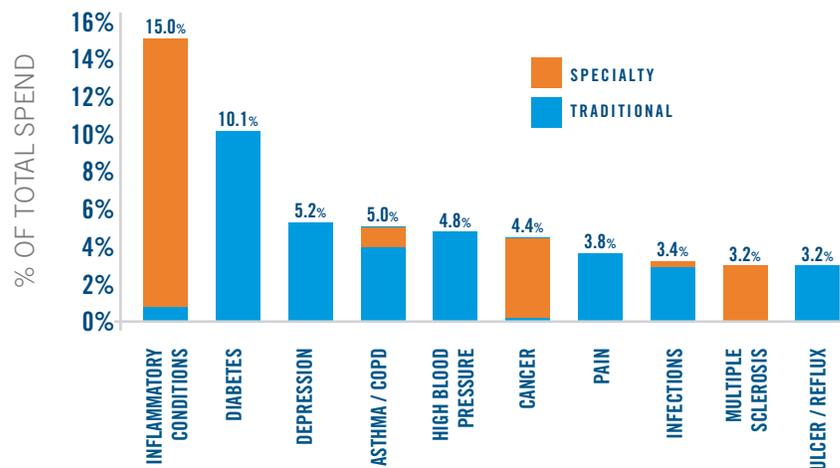
The three medications that led spending in 2018 were specialty drugs used to treat inflammatory conditions. Infliximab, adalimumab and ustekinumab made up more than 10% of the overall total.

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® / Fozquest™	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.

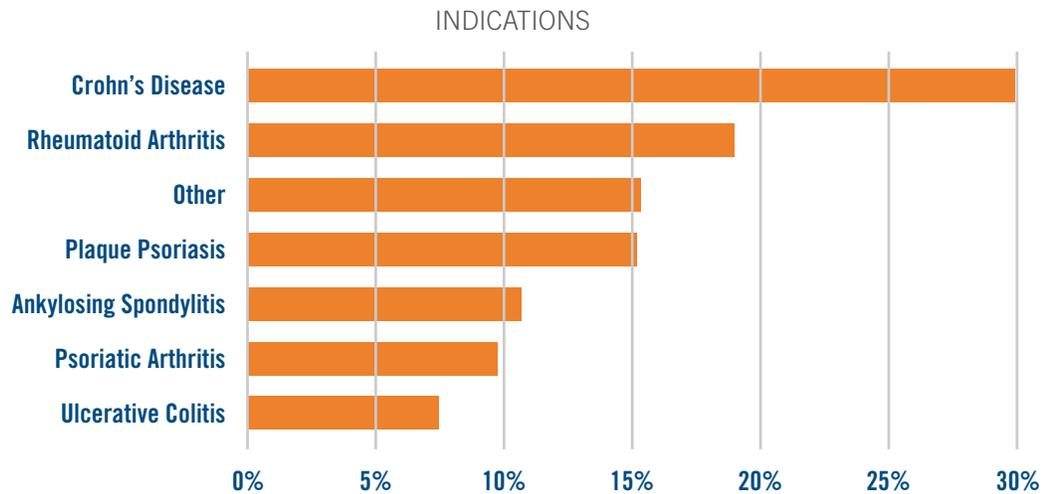
A new biologic, Siliq™ (brodalumab), was approved in 2018 for use in moderate to severe plaque psoriasis. Siliq is the third interleukin-17 inhibitor approved for psoriasis. The mechanism of action for Siliq, an interleukin-17 receptor antagonist, is distinct from the other drugs in this class, Cosentyx®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

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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 Diamicon® (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).

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- **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® (semaglutide), 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

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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%

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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	Ciprallex®	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, Fasentra™ (benralizumab), was approved in early 2018. An adjunct therapy, Fasentra 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/salmeterol) 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.

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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.

SECTION 2 – A LOOK AT THE OVERALL DRUG TREND FOR 2018

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.

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- 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).

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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%

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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.

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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.

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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%