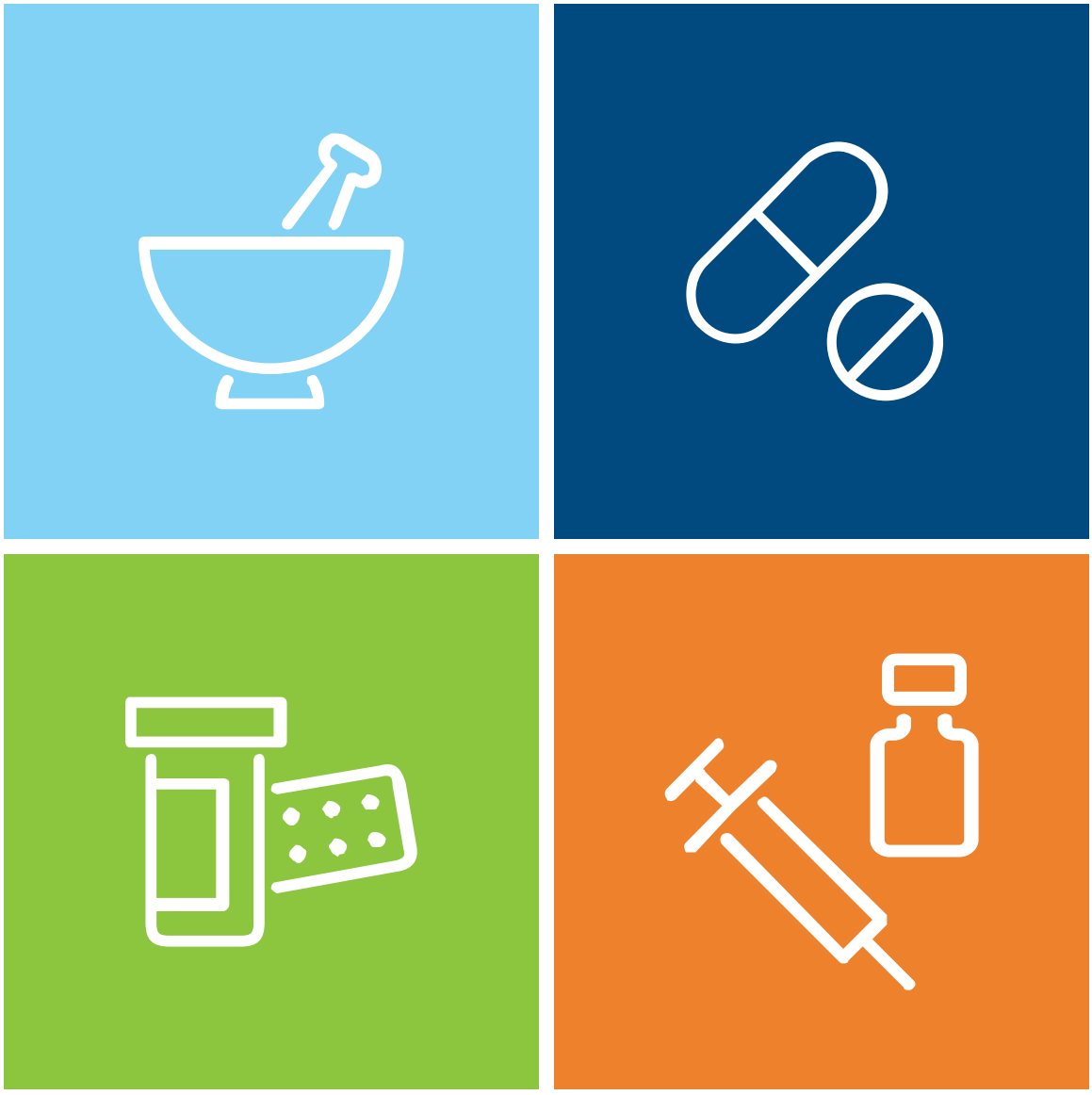
EXPRESS SCRIPTS CANADA

DRUG PIPELINE REPORT



EXPRESS SCRIPTS®

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INTRODUCTION

Health Canada continuously reviews new medications and it concluded its review of 47 new drugs in the first half of 2021. While much of the focus this year was spent on emerging therapies for COVID-19, there are many other medications that are projected to have a significant effect on prescribing practices. As these emerging developments have the potential to impact private drug plans, it is important to look prospectively at drugs coming down the pipeline and for submission to Health Canada in the near future.

New, innovative research in diabetes shows molecules with the potential to delay the onset of Type 1, new drug classes, and additional therapies for diabetes complications. Three potential new treatment options for Alzheimer's disease have emerged, as well as two potentially impactful options to treat psoriasis. As such, this quarter's pipeline report will focus on promising treatments for diabetes, psoriasis, and Alzheimer's disease, as well as touch on some biosimilar news.

UPCOMING BIOSIMILARS

Common Name	Biologic Reference Drug	Therapeutic Area	Submission dates[1] to Health Canada	Estimated Impact on Private Plans[2]
Adalimumab	Humira®	Immunosuppressants	2021-02 2021-03	Moderate
Bevacizumab	Avastin®	Antineoplastic agents	2020-07 2020-10 2021-02	Low-moderate
Etanercept	Enbrel®	Immunosuppressants	2020-02	Low-moderate
Filgrastim	Neupogen®	Immunostimulants	2019-03	Low
Human insulin (recombinant)	Humulin®	Drugs used in Diabetes	2021-05	Low-moderate
Infliximab	Remicade®	Immunosuppressants	2021-02	Moderate
Insulin aspart	NovoRapid®	Drugs used in Diabetes	2020-12	Low-moderate
Insulin glargine	Lantus®	Drugs used in Diabetes	2021-06	Low-moderate
Ranibizumab	Lucentis®	Opthalmologicals	2021-05	High
Trastuzumab	Herceptin®	Antineoplastic agents	2020-04	Low

[1] Different manufacturers' submissions pending review
[2] Impact estimated based on number of marketed biosimilars, claims for the reference brand, and annual drug cost.

Most biosimilars submitted to Health Canada for review already have biosimilar competitors in the market with the exception of ranibizumab, the first biosimilar for Lucentis®. This will soon be on the market and indicated to treat conditions related to vision impairment. This is anticipated to help reduce spend on Lucentis®, as well as potentially Eylea® (aflibercept). The annual cost of Lucentis® in the first year of treatment is approximately $19,000.

Biosimilars are now available for a significant number of insulin products; however, interchangeability has been a barrier to uptake. Patients are required to obtain a new prescription for the biosimilar in order for the pharmacist to dispense the medication. Recently the FDA approved an insulin glargine biosimilar (Semglee™) that will be interchangeable without the intervention of the prescriber for the reference brand. This interchangeability would ease the path to the cost savings associated with insulin biosimilars. It will be interesting to see if Health Canada will take a similar approach to assessing the next biosimilars.

WHAT'S COMING

Alzheimer's

An estimated 76,000 Canadians are diagnosed with dementia every year. There has been much excitement surrounding new anti-amyloid therapies to treat Alzheimer's which may change the course of the disease. Previously only symptomatic treatments were available for patients afflicted by this debilitating condition. Anti-amyloid therapies are monoclonal antibodies administered intravenously which is a significant deviation from the traditional oral medications currently used to treat the symptoms of Alzheimer's. These new therapies target the formation of amyloid plaques thought to be responsible for the progressive cognitive decline associated with the disease. The last new drug entrants for Alzheimer's date back to the early 2000s. Trials in this therapeutic area have been plagued by failures and reduced research investment and resulted in 20 years of stagnation.

Aducanumab (brand Aduhelm®) was approved in July 2021 by the U.S. Food and Drug Administration (FDA) for mild cognitive impairment and mild dementia amid controversy. Trials for this drug were halted early after analysis showed benefits were unlikely. It was only after re-analysis of the data where a subset of patients was found to benefit from therapy that it was once again submitted to the FDA and finally approved. The benefit of aducanumab was measured using the number of the disease-causing amyloid plaques in the brain, an unestablished surrogate marker of the actual cognitive decline associated with Alzheimer's Disease.

> New anti-amyloid therapies to treat Alzheimer's may change the course of the disease.

The pathway to approval in Canada remains uncertain. An accelerated pathway normally reserved for cancer drugs was used to approve aducanumab in the U.S. This accelerated pathway is used for drugs that are only reasonably likely to help patients and does require the manufacturer to perform additional evaluations. Disagreement with the FDA's decision has resulted in resignations by key members of the advisory board who voted against its approval. Combining this with the use of an unestablished endpoint of amyloid plaque levels, the approval is marred by outstanding questions on the true degree of benefit.

Aducanumab is administered by IV infusion every four weeks. MRIs are required at specific dosing intervals to monitor for emerging safety concerns associated with amyloid-related imaging abnormalities such as microhemorrhage or edema. These are most common within the first eight doses and are mostly asymptomatic, hence the need for ongoing MRIs during treatment. In addition to the drug cost, ongoing PET scans are required to determine the patient's amyloid plaque count. Currently available drug therapies do not require this level of monitoring.

Based on the FDA-approved indication, the recommended patient population should only be those in the very early stages of the disease. However, the patient population that could benefit most from aducanumab is still unclear. Despite this advancement and upcoming new treatment options, early diagnosis and research into early markers of disease remains critical.

Two other biologic options in this class have received breakthrough therapy designations from the FDA: lecanemab (Eisai and Biogen) and donanemab (Eli Lilly). Phase 3 trials are pending for both lecanemab and donanemab after Phase 2 trials demonstrated a reduction in cognitive and functional decline compared to placebo. Pricing information is pending for these investigational alternative therapies.

Aducanumab was submitted for review to Health Canada, the other biologic options have not been submitted at this time.

	Traditional Alzheimer's Disease Medications	Disease-modifying Therapy
Drug Classes	Cholinesterase Inhibitors	Anti-myeloid therapy
Dosage Form	Oral or transdermal	IV injection
Drug Examples	Donepezil	Aducanumab
Mechanism	Limited to symptom management	Disease-modifying by preventing formation and reducing amyloid plaques
Annual Cost	$200	Approx. $50,000 USD*
Private Payer Impact	Highly genericized medication class	Likely stringent prior authorization criteria

* Pricing is not yet available in Canada

Autoimmune Disorders

Autoimmune disorders, including rheumatoid arthritis, Crohn's disease and psoriasis, are a focus of intense research. Biologic therapies already exist for the treatment of these conditions; however, further enhancements in the effectiveness of new molecules offers promise to individuals suffering from these conditions. In this report, we focus on a few psoriasis drugs in the pipeline.

Autoimmune disorders are a focus of intense research.

Bimekizumab

Psoriasis affects approximately one million Canadians. While there are many biologic medications used to treat moderate to severe plaque psoriasis, UCB's bimekizumab, which was submitted for review to Health Canada in April 2021, is a promising new option.

This new biologic immunosuppressant demonstrated superiority in a head-to-head comparison versus Janssen's Stelara® (ustekinumab). Eighty-five percent of patients treated with bimekizumab had achieved 90% skin clearance (PASI 90) at week 16. 59% of patients benefitted from complete skin clearance (PASI 100). Stelara® achieved a PASI 90 in 50% of patients and 21% of patients achieved a PASI 100. Similar results were seen when comparing bimekizumab to adalimumab, which is another commonly prescribed biologic drug used to treat psoriasis.

Furthermore, in July 2021, a phase 3b study demonstrated the superiority of bimekizumab when compared to Novartis' Cosentyx® (secukinumab) for complete skin clearance when compared at weeks 16 and 48.

These results are compelling to dermatologists and their patients, as bimekizumab significantly outperforms the top biologics used to treat plaque psoriasis. With a pre-approval from the UK's National Institute for Health and Care Excellence (NICE) and the FDA, an approval from Health Canada is likely. More indications are expected in the near future as psoriatic arthritis trials are underway.

Deucravacitinib

Another upcoming medication to treat moderate to severe plaque psoriasis is Bristol Myers Squibb's deucravacitinib. This tyrosine kinase 2 (TYK2) inhibitor is an oral treatment that outperformed Amgen's Otezla® (apremilast), another oral treatment in clinical trials. In POETYK PSO-1, 58.7% of patients at week 16 who received deucravacitinib achieved at least 75% skin clearance (PASI 75) compared with 35.1% of patients who received apremilast. Similar results were seen in POETYK PSO-2. These results suggest that deucravacitinib is more effective than apremilast and some experts believe its efficacy is comparable to Enbrel® (etanercept).

To date, if approved, deucravacitinib would be the safest and most efficacious oral option available to treat plaque psoriasis with the potential to expand its uses to other autoimmune diseases. Phase 3 trials using deucravacitinib in psoriatic arthritis are already demonstrating efficacy. Deucravacitinib is an option for physicians and patients who want a convenient and effective oral option with a similar safety profile to that of a biologic.

Microbiome-Targeting Therapies

An interesting research path in autoimmune disorders, such as psoriasis, is focused on microbiomes. The skin and gastrointestinal (GI) tract are naturally colonized by bacteria, or microbiomes. Since imbalances of the microbiome can contribute to immunological diseases, scientists are attempting to restore healthy balances of bacteria using microbiome therapies (MBT). There are over 20 MBTs currently under development for GI (Crohn's disease, ulcerative colitis, irritable bowel syndrome), dermatological (acne, psoriasis, atopic dermatitis), and respiratory conditions.

MBTs are a long way from being approved – mostly in the Phase 1 and 2 trials and represent a paradigm shift in treatment. MBTs have unique mechanisms of action, for example an oral drug for irritable bowel syndrome (IBS), which contains strains of a bacteria *Blautia hydrogenotrophica*. This therapy may improve the biodiversity in the gut and address some of the causative factors of IBS symptoms.

Diabetes

Ground-breaking research in the delay of the onset of Type 1 Diabetes is underway as well as new drug classes and additional therapies to prevent complications from diabetes.

Groundbreaking research underway

Research

Teplizumab is a monoclonal antibody currently under investigation for its potential to delay the onset of Type 1 diabetes (T1D). Phase 2 trials of teplizumab involved screening children with first-degree relatives with Type 1 diabetes.

Patients tested for diabetes-related autoantibodies were included in the trial of teplizumab. This Phase 2 trial found that treatment with teplizumab delayed the onset of T1D by a median of three years.

Typically, patients testing positive on screening would be monitored on a regular schedule using glucose-tolerance tests. However, only 15% of T1D patients have a relative with T1D and therefore, a significant patient population would not be identified by this screening and consequently, would not be candidates for this drug.

New Drug Classes

Tirzepatide belongs to a new drug class in therapies for Type 2 diabetes: a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. The dual action is proposed to have a synergistic effect, resulting in greater improvement in blood glucose levels and body weight reduction than GLP-1 agonists alone. GLP-1 agonists like semaglutide and dulaglutide have become popular choices amongst prescribers and patients alike due to convenient dosing (i.e., one injection per week) and weight reduction and markers of blood glucose control like A1C. Tirzepatide is also a once weekly subcutaneous injection.

Phase 3 studies have demonstrated that tirzepatide has positive results on A1C and body weight reduction. After 40 weeks of treatment, patients receiving the tirzepatide 15 mg dose lost an average of 11.2 kg of body weight and A1C reduction of 2.3%. In the same trial, once weekly semaglutide resulted in a 5.7 kg weight loss and 1.86% reduction in A1C. Semaglutide represented the highest spend for non-specialty drugs in our latest **Prescription Drug Trend Report**.

New drug class outperforms popular GLP-1 agonists

Trials are now assessing the effects on cardiovascular outcomes like heart attack and stroke between tirzepatide to dulaglutide, another GLP-1 agonist. Tirzepatide will likely be submitted for FDA approval in the coming months and has not been submitted to Health Canada for review at this time. Positive outcomes compared to the GLP-1 agonists alone may influence a higher price tag compared to this established class. Future studies are also evaluating tirzepatide as a potential treatment for non-alcoholic steatohepatitis (NASH) and heart failure with preserved ejection fraction (HFpEF).

Additional Therapies for Diabetic Macular Edema

Therapies are also evolving in the treatment of the complications associated with diabetes. These complications, including damage to the small blood vessels of the eyes are the focus of research into new molecules and new indications for an existing drug.

- Beovu®, the newest VEGF therapy for ophthalmic conditions, has demonstrated promising outcomes in the treatment of diabetic macular edema. Trial results showed it was non-inferior to comparator Eylea®. If approved by Health Canada, Beovu® would join Lucentis® and Eylea® for this indication with potentially fewer injections. Currently, this drug has only been approved for the treatment of neovascular (wet) age-related macular degeneration (AMD).
- Further down in the pipeline is an oral investigational drug for the treatment of diabetic macular edema – a plasma kallikrein inhibitor. Studies are preliminary and Phase 2 studies are only beginning despite the potential to change the paradigm to treat this common condition associated with diabetes.

CONCLUSION

In the next few years, innovation will come to Canada in crowded therapy spaces including psoriasis and diabetes. We will also see some controversy in areas such as Alzheimer's disease, which hasn't seen any advancements for quite some time.

The Alzheimer's space, which has not had an advancement in decades, may have three potential new treatment options. While aducanumab is surrounded by controversy, lecanemab and donanemab could be promising new options. Outstanding questions related to long-term safety and the targeted patient population remain unanswered.

Advancements in the treatment of psoriasis, a condition that affects approximately one million people, have the potential to help many Canadians. Bimekizumab, a biologic with compelling efficacy results, is sure to make a splash in this space once it receives approval from Health Canada. Deucravacitinib, an efficacious oral option, may see physicians switch to this molecule as initial systemic therapy over Otezla®.

Revolutionary research in diabetes shows teplizumab has the potential to delay the onset of Type 1 diabetes and another agent, tirzepatide, demonstrates the potential to improve A1C and reduce body weight. Finally, additional therapies to treat diabetic macular edema are also in the pipeline.

It is imperative to monitor these new molecules as they are likely to be costly and their approval by Health Canada can shift prescribing habits and lead to a substantial financial impact on private plans.

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