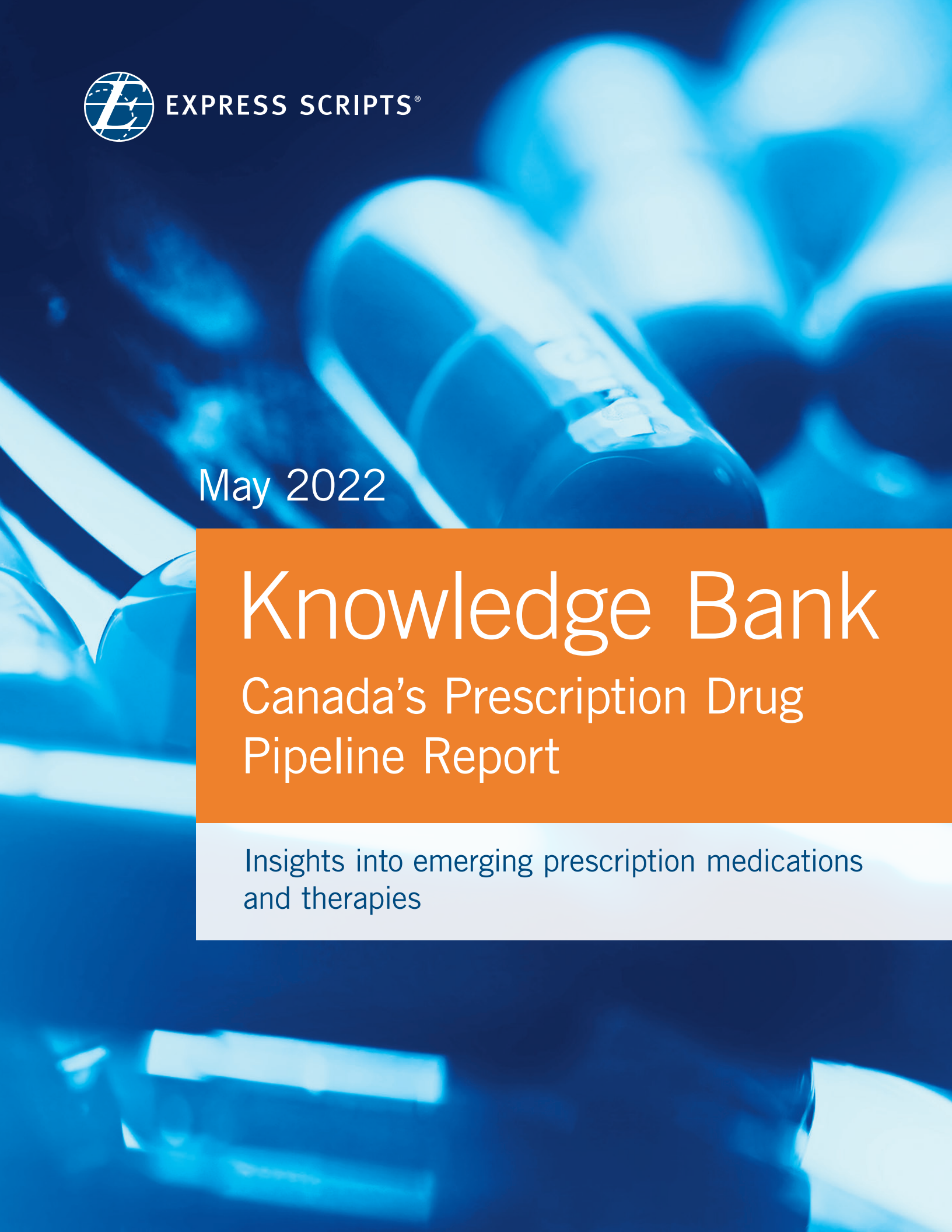

EXPRESS SCRIPTS®

May 2022

Knowledge Bank

Canada's Prescription Drug Pipeline Report

Insights into emerging prescription medications and therapies

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INTRODUCTION

Express Scripts Canada (ESC) is pleased to launch our new quarterly report, *Knowledge Bank – Canada's Prescription Drug Pipeline Report*. We continue to focus on the emerging treatments that may have the greatest impact on private plans. We hope you enjoy the new format.

Included in this first report of 2022 are updates to the developments discussed in ESC's inaugural Pipeline Report: significant updates in price and availability of the controversial treatment for dementia and ongoing monitoring of biosimilar submissions to Health Canada.

This quarter's report highlights developments in two prevalent conditions: migraine headache treatments under review by Health Canada and a potential game-changer in helping children with peanut allergies.

Rounding out the update is a glance at the ongoing evolution of gene therapies. Gene therapies are not new to Canada, but the spectrum of diseases where these treatments are being investigated continues to evolve. The focus of this report is on the upcoming gene therapies being studied in rare hereditary blood disorders.

UPDATE FROM OUR LAST REPORT

Biosimilars

Common Name	Biologic Reference Drug	Therapeutic Area	Submission dates to Health Canada	Estimated Impact on Private Plans[1]
Enoxaparin sodium	LOVENOX®	Antithrombotic agents	2021-12	Low
Etanercept	ENBREL®	Immunosuppressants	2020-02	Low-moderate
Human insulin (recombinant)	HUMULIN®	Drugs used in diabetes	2021-05	Low-moderate
Insulin glargine	LANTUS®	Drugs used in Diabetes	2021-06	Low-moderate
Ranibizumab	LUCENTIS®	Opthalmologicals	2021-05	High
Trastuzumab	HERCEPTIN®	Antineoplastic agents	2021-08	Low

[1] Impact estimated based on the number of marketed biosimilars, claims for the reference brand, and annual drug cost.
Reference: Reference data available upon request.

In an update from our previous report, Health Canada is currently reviewing six biosimilars. This still includes the ranibizumab biosimilar, which as discussed in our last issue, is anticipated to help reduce spend on LUCENTIS®, as well as potentially EYLEA® (aflibercept).

Alzheimer's

Express Scripts Canada's first Pipeline Report discussed the new agent for Alzheimer's approved in the U.S. This new class of medications represented a new mechanism of agent to treat Alzheimer's, and represents a significant update after some stagnation in this therapeutic area. The manufacturer announced a reduction in the price of ADUHELM® (aducanumab) by 50% in December 2021, bringing the price down to $28,200.

Following FDA approval, the highly anticipated decision on funding through Medicare (coverage for U.S. seniors) came through in January 2022. The Centers for Medicare and Medicaid Services proposed to cover these amyloid treatments only for patients who are in approved randomized controlled studies conducted in hospital-based outpatient settings. Clinical trial participants must have a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild dementia and have evidence of amyloid plaques. This decision limits the eligible population, but it reflects the uncertainty in the evidence supporting these therapies. Clinical trials should generate more evidence need to fully support the therapeutic effects of these medications.

COMING SOON

Migraine

Spend on medications for the prevention of migraines has increased in the past few years (see Drug Trend Report 2021), mainly due to the availability of new injectable CRGP inhibitor therapies which can prevent migraines. A new class, with a similar mechanism, but which can be taken orally, has been making an impact on the U.S. market. These molecules are currently under review by Health Canada.

Injectable CGRP inhibitors are monoclonal antibodies and therefore must be injected because of their size. Gepants are a class of CGRP inhibitors that are smaller in molecular size and therefore can be dosed orally. Oral therapies may be preferred for some patients due to convenience and avoidance of needles. Three gepants have been approved by the FDA, providing some clinical and market experience as we await these to be reviewed and approved by Health Canada.

Unlike injectable options, the gepants have been approved for both prevention of migraines and treatment at the onset of a migraine. The gepants have advantages over usual first-line acute treatments – triptans – including better tolerability and since the gepants do not cause vasoconstriction and are therefore safer in patients with cardiovascular disease.

Some initial clinical experience has noted that patients may not respond equally to the injectable and oral options. Therefore, the oral options haven't become the clear-cut advantageous option that was expected. U.S. data shows that sales of the injectable options have plateaued while the oral gepants have shown growth due to use for the treatment at onset of a migraine.

There are no head-to-head comparison trials at this time between the oral and injectable options. There is some discussion that the injectable antibody therapies may remain the preferred option due to durable response and less frequent dosing. These oral agents could also be favourable among patients with patterned migraine attacks for example when prophylaxis is required during predictable situations.

Interestingly, the annual price of the oral preventative therapy in the U.S. is higher than that of the injectable agents. Pricing of these agents will be significant in coverage decisions.

Molecule	Indication: Migraine Prevention or Acute Treatment at Onset	Dosing
Atogepant	Preventative	Daily
Rimegepant	Acute and preventative	Every other day
Ubrogepant	Acute	As needed

The first gepant approved by the FDA was rimegepant, which has not been submitted to Health Canada for approval. This oral disintegrating tablet approved for both prevention and acute treatment offers further convenience to patients who can use the same medication for prevention and treatment of a migraine.

Atogepant and ubrogepant are under review by Health Canada. Atogepant will be available in multiple strengths, providing further flexibility to prescribers.

Atogepant and ubrogepant were submitted to Health Canada for review in 2021 and approval may come in 2022.

FURTHER DOWN THE LINE

PALFORZIA®

Some parents may have breathed a slight sigh of relief as a drug by the name of PALFORZIA® became the first approved peanut allergy therapy in the U.S. and Europe when it was approved by the FDA in 2020 and the European Commission in 2021. PALFORZIA® helps to reduce the severity of allergic reactions to peanuts with patients aged 4 to 17 years old. The medication comes as a powder sachet that can be emptied onto semisolid food for the patient to ingest.

A study conducted in the U.S., Canada and Europe showed that approximately 67% of participants were able to tolerate a 600 mg dose of peanut protein with no more than mild allergic symptoms after six months of maintenance treatment. The road to the maintenance phase of treatment, however, can be long as it only begins after months of slowly increasing dosing levels.

With approximately 2 in 100 children in Canada having a peanut allergy (3.2% of children aged 0-17), PALFORZIA® may make a splash when it comes to Canada.

Gene Therapies

It is only a matter of time before gene therapies play a major role in the way patients are treated. These therapies are given to patients only once but can be life changing for them. Of course, this benefit comes with significant costs associated with it, primarily due to manufacturing and administration challenges. Currently only three gene therapies have been approved in Canada: LUXTURNA®, ZOLGENSMA®, and KYMRIAH®.

Some gene therapies coming to the U.S. before they make their way to Canada are ROCTAVIAN® (valoctogene roxaparvovec), etranacogene dezaparvovec, betibeglogene autotemcel, and LENTIGLOBIN® (lovotibeglogene autotemcel).

Blood Disorders

Hemophilia

Hemophilia A and hemophilia B are rare hereditary disorders, in which patients are deficient in a coagulation factor, which leads to bleeding and deficiencies in clotting. Gene therapy is an attractive option for these patients as the missing gene can be replaced into cells and can produce the deficient protein factor.

BioMarin's ROCTAVIAN® would be the first gene therapy available for severe hemophilia. ROCTAVIAN® was rejected by the FDA in 2020 as they requested a 2-year follow-up for the Phase III trial to evaluate its efficacy and safety. As the results of the follow-up come in, BioMarin will be resubmitting its FDA application in the first half of 2022.

Another gene therapy for hemophilia is on its way from biotech company uniQure. In a phase 3 trial, etranacogene dezaparvovec showed promising results in treating patients with severe hemophilia B. Patients were seen to have sustained effect even a year post-infusion. It was put on hold as a patient had developed hepatocellular carcinoma, but the hold was lifted once the FDA concluded it was unlikely that gene therapy was to have caused it.

Thalassemia

Thalassemia is an inherited blood disorder caused by a reduced production of hemoglobin leading to ineffective production of red blood cells, anemia, and iron overload. Therapy currently centers around frequent blood transfusion and hematopoietic cell transplantation.

For patients with beta-thalassemia who require regular red blood cell transfusions, betibeglogene autotemcel from biotech company, Bluebird Bio is a promising option. The European commission has already granted conditional marketing authorization for patients 12 and up. As for the U.S., it was originally rejected by the FDA, but the application was resubmitted September 2021 and it was granted a priority review with an action date of May 20, 2022.

Sickle Cell Anemia

Bluebird Bio's LENTIGLOBIN® is also touted to be a promising option for the treatment of sickle cell anemia. Sickle cell anemia is an inherited blood disorder in which the shape of red blood cells is affected caused by a defect in hemoglobin itself. LENTIGLOBIN® was originally put on a clinical hold by the FDA as a patient developed acute myeloid leukemia and another developed myelodysplastic syndrome, but the hold has since been lifted in June 2021.

CONCLUSION

The migraine treatment space continues to evolve. Emerging oral preventative medications may offer more convenient options to patients. The oral gepants for migraine treatment could potentially replace the widely genericized triptans. While these treatments remain under review by Health Canada, these have been approved in the U.S. since 2019, offering additional insight and real-world practice experience.

Several gene therapies are under review for blood disorders, offering potential for life-altering treatments to these genetic hereditary conditions.

Pipeline drugs this quarter range from alternative treatments for the prevalent conditions like migraine to gene therapies for rare conditions that affect only a small number of Canadians. Therapies at both ends of this spectrum have the potential for substantial financial impact on private plans.

References: Reference data available upon request.

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