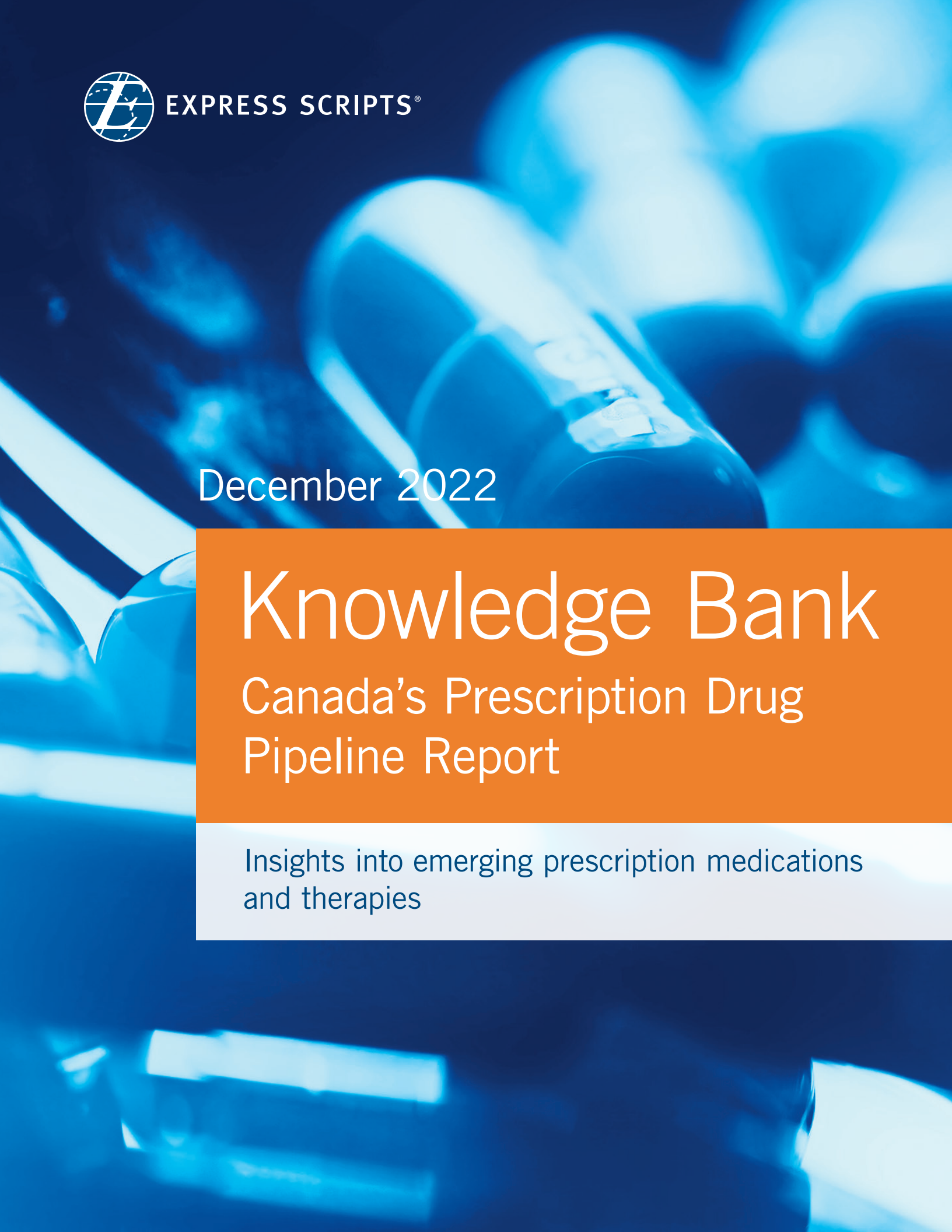

EXPRESS SCRIPTS®

December 2022

Knowledge Bank

Canada's Prescription Drug Pipeline Report

Insights into emerging prescription medications and therapies

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INTRODUCTION

We are pleased to publish the final report of Express Scripts Canada's Knowledge Bank for 2022 – Canada's Prescription Drug Pipeline Report. In this issue, we continue our focus on emerging treatments in Canada that will have the greatest impact on private plans.

This report highlights a new and emerging drug class that offers a wide range of applications, and has garnered considerable research and development interest: bispecific antibodies. We discuss its growth and several upcoming drugs in the global pipeline drug development.

Included in the report are ongoing monitoring of biosimilar submissions under review by Health Canada and breakthrough results on another drug contender for Alzheimer's disease.

Rounding out our updates in this issue, we look at innovative drug targets in development for the treatment of diabetes, obesity, and Alzheimer's Disease.

UPDATE FROM OUR LAST REPORT

Biosimilars

Common Name	Biologic Reference Drug	Therapeutic Area	Submission dates to Health Canada	Estimated Impact on Private Plans*
Aflibercept	EYLEA®	Opthalmological	2022-05	High
Bevacizumab	AVASTIN®	Antineoplastic agents	2022-03	Low
Eculizumab	SOLIRIS®	Immunosuppressants	2022-07	Low
Enoxaparin sodium	LOVENOX®	Antithrombotic agents	2022-09	Low
Pegfilgrastim†	NEULASTA®	Immunostimulants	2022-05	Low
Trastuzumab	HERCEPTIN®	Antineoplastic agents	2021-08	Low

* Impact estimated based on the number of marketed biosimilars, claims for the reference biologic drug, annual drug cost, and if part of a publicly funded program.

† There are two pegfilgrastim biosimilar submissions under review.

In an update from the previous report, Health Canada is currently reviewing 7 biosimilars. A new enoxaparin biosimilar was submitted for review, replacing the spot left by the recent approval of ELONOX® on September 2022 as the fourth biosimilar for LOVENOX® (enoxaparin sodium).

Lecanemab and Alzheimer's Disease

As seen with the fate of aducanumab, finding an effective treatment that could slow the progression of Alzheimer's disease has been full of disappointments. However, a momentous breakthrough with lecanemab offers a hopeful turn in this field. Recently, Eisai revealed that treatment with lecanemab was associated with statistically significant results in reducing cognitive and functional decline by 27% from its global Phase III trial. Pricing for lecanemab has not yet been disclosed, but annual costs are estimated to be similar to aducanumab, which is marketed in the US at US$56,000 per year. Safety risks concerning bleeding in the brain may challenge lecanemab's uptake, where two deaths related to a brain bleed occurred in patients receiving treatment during its extension study. Lecanemab is still under priority review by the FDA and there is no submission Health Canada at this time.

COMING SOON

Bispecific antibodies

Bispecific antibodies (bsAbs) have become an increasingly rapid area of therapeutic interest in the last few years, with over 200 bsAbs in preclinical and clinical stages of drug development. A recent market research report revealed that the bsAb market has experienced a high growth rate since 2016, surpassing US$9 billion in the first quarter of 2022 in cumulative sales.[1] Of note, VABYSMO®, which was approved in the US in January 2022, has reached close to US$2.96 billion in sales within 9 months of its launch, with 60% of its sales coming in from the third quarter.

At the time of this report, there are nine bsAbs marketed worldwide, where six bsAbs are marketed in Canada (*Table 1*) with the last three being approved in 2022.

BsAbs are antibodies engineered to bind to two different antigens or epitopes (part of an antigen capable of stimulating an immune response) at the same time, targeting multiple disease specific signalling pathways and thus, improving clinical efficacy over monoclonal antibodies. Huge advancements in antibody development brought forth a variety of bsAb designs or *formats*, making them highly versatile, with broad treatment applications in cancer and other complex diseases.

Table 1: Approved Bispecific Antibodies in Canada and the United States

Bispecific Antibody Drug Approvals						
Company	**Trade Name**	**Drug Name**	**Indication**	**Health Canada Approval**	**Health Canada Market date**	**FDA Approval**
Trion Pharma	REMOVAB®	Catumaxomab	Malignant ascites	May 2012	Cancelled Premarket 2018	Not approved
Amgen	BLINCYTO®	Blinatumomab	Relapsed or refractory (R/R) precursor B-cell acute lymphoblastic leukemia (ALL)	Dec 2015	Mar 2016	Dec 2014
Roche/ Genentech	HEMLIBRA®	Emicizumab	Reduce or prevent bleeding due to Hemophilia A	Aug 2018	Oct 2018	Nov 2017
Janssen	RYBREVANT®	Amivantamab	Non-small cell lung cancer	Mar 2022	Apr 2022	May 2021
Roche/ Genentech	VABYSMO®	Faricimab	Wet age-related macular degeneration and diabetic macular edema	May 2022	Jul 2022	Jan 2022

[1] Chawla, N. Global Bispecific Antibody Market Opportunity, Drug Sales, Price and Clinical Trials Insight 2028. Kuick Research, Aug 2022. https://www.kuickresearch.com/report-global-bispecific-antibodies-antibody-market-size-blincyto-hemlibra-rybrevant-sales

Table 1: Approved Bispecific Antibodies in Canada and the United States (continued)

Bispecific Antibody Drug Approvals (continued)						
Company	**Trade Name**	**Drug Name**	**Indication**	**Health Canada Approval**	**Health Canada Market date**	**FDA Approval**
Immunocore	KIMMTRAK®	Tebentafusp	Unresectable or metastatic uveal cancer	June 2022	Aug 2022	Jan 2022
Janssen	TECVAYLI®	Teclistamab	R/R multiple myeloma	—	—	Oct 2022
Roche/ Genentech	LUNSUMIO®	Mosunetuzumab	R/R follicular lymphoma	—	—	In priority review

The majority of bsAbs in the pipeline are in blood/bone marrow cancers and solid tumours, but there are many early-phase clinical trials ongoing for infectious diseases, diabetes, Alzheimer's disease, and other inflammatory conditions.[2] The pursuit of this treatment pathway will be interesting to follow as we discuss some bsAbs of interest below.

Hematology

Two new bsAbs (teclistamab and mosunetuzumab) are making waves after BLINCYTO® (blinatumomab) – the first bsAb approved and marketed in the hematology space in 2015 (see *Table 1*, previous page).

Teclistamab received FDA approval on October 25, 2022 for the treatment of R/R multiple myeloma and is available as a subcutaneous administration. It is a first-in-class, BCMA x CD3 bispecific T-cell engaging bsAb. It binds to both the B-cell maturation antigen (BCMA) expressed on the surface of multiple myeloma cells and CD3 on the surface of immune cells, which recruits T-cells to surrounding tumour cells for a targeted attack. Its pivotal phase II trial demonstrated an overall response rate of 63% in patients who had received a median of five previous lines of therapy.[3]

Meanwhile, Genentech's mosunetuzumab has been granted priority review by the FDA for its R/R Follicular Lymphoma indication in July 2022. Mosunetuzumab is a CD20 x CD3 T-cell engaging bsAb, and is currently one of the most competitive bsAb target combinations. In clinical trials, mosunetuzumab demonstrated high complete response rates and was well tolerated in patients who received two or more prior lines of therapy.[4] Its pipeline portfolio is extensive, containing multiple phase I to III clinical trials in various hematological indications from B-cell lymphomas to chronic lymphocytic leukemia.

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[2] Ma, Jiabing et al. Bispecific Antibodies: From Research to Clinical Application. Frontiers in immunology vol. 12 626616. 5 May 2021, doi:10.3389/fimmu.2021.626616

[3] Moreau, Philippe et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. The New England journal of medicine vol. 387,6 (2022): 495-505. doi:10.1056/NEJMoa2203478

[4] Budde, Lihua E et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. The Lancet. Oncology vol. 23,8 (2022): 1055-1065. doi:10.1016/S1470-2045(22)00335-7

With the efficacy and tolerability of bsAbs demonstrated thus far in trials, they could become a feasible alternative to CAR-T cell therapies reserved for later lines of therapy. Furthermore, bsAbs carry less logistical and institutional challenges than available CAR-T cell therapies and could be administered in an outpatient setting. At the time of this report, there are no submissions under review for either teclistamab or mosunetuzumab at Health Canada.

Obesity and Non-Alcoholic Fatty Liver Disease (NAFLD)

Another Genentech pipeline bispecific antibody, BFKB8488A, is currently entering its phase II trial as a possible treatment for patients with NAFLD. This condition affects approximately 70% of patients with Type 2 diabetes mellitus and occurs when there is a build-up of excess fat in the liver cells, causing liver damage.

BFKB8488A targets both fibroblast growth factor receptor 1c (FGFR1c) which is important in energy expenditure and metabolism, as well as its coreceptor β klotho (KLB) expressed mainly in fat, liver, and pancreatic cells. Early phase trial results showed improvements in liver function, lipid parameters, and liver fat content. Additionally, in overweight and obese patients, subcutaneous BFKB8488A resulted in a dose-dependent decrease in body weight and exhibited reduced cravings for sweet foods.[5] Antibody activation of FGFR1 and KLB complex could be a possible pharmacological target for the treatment of obesity and NAFLD.

Rheumatoid Arthritis (RA)

The pathogenesis and treatment of RA was revolutionized with the advent of monoclonal antibodies (mAbs), primarily anti-TNFα agents such as adalimumab. Ablynx has developed a unique type of bispecific antibody called NANOBODY® consisting of only the target-binding fragments of mAbs, resulting in high tumour tissue permeability due to their low molecular weight. Ozoralizumab is a multivalent NANOBODY-based bsAb that has two TNFα nanobodies and an anti-human serum albumin nanobody. It was developed to maintain drug levels in a therapeutic range, minimizing the formation of anti-drug antibodies responsible for the weaning efficacy of mAbs over time.

It received its first global approval in Japan in September 2022 and is a promising candidate not only for treatment-naïve patients but also in patients who have failed previous anti-TNFα treatment. At the time of this report, there is no submission under review at Health Canada.

[5] Baruch, Amos et al. Antibody-mediated activation of the FGFR1/Klothoβ complex corrects metabolic dysfunction and alters food preference in obese humans. Proceedings of the National Academy of Sciences of the United States of America vol. 117,46 (2020): 28992-29000. doi:10.1073/pnas.2012073117

FURTHER DOWN IN DEVELOPMENT

Diabetes

Early clinical trials are investigating a first-in-class covalent menin inhibitor, which may have a direct effect on beta cell preservation and regeneration. Preserving the insulin-secreting beta cells of the pancreas is key to the pathophysiology and complications of diabetes. Clinical trials involving patients with diabetes are notably taking place in Canada with results expected in the first half of 2023.

Therapies available to date haven't been able to directly regenerate these critical beta cells, making this a groundbreaking approach to treating diabetes.

Obesity

There is heightened attention on medications used to treat obesity due in part to the recent approval of the semaglutide formulation specifically indicated for weight management. We continue to follow relevant updates in this therapeutic area including the surveillance of novel agents.

Research is ongoing into amylin analogues, which can be used either as monotherapy or co-formulated with GLP-1 agonists, such as semaglutide. Amylin is secreted alongside insulin from the pancreas and acts as a satiety signal for the brain. Therefore, the use of amylin analogues may result in reduction of food intake and consequently, weight loss. Study results of a novel agent show that the combination with semaglutide in early trials led to an increased weight loss compared to use of the individual agents as monotherapy. Further trials will be needed to confirm the safety and efficacy in larger populations.

Alzheimer's Disease

A new formulation of the drug istradefylline is being investigated for its use in Alzheimer's disease. Istradefylline targets adenosine receptors in the brain, which may be implicated in memory impairment. This molecule is structurally related to caffeine, which has already demonstrated some effect on concentration in Alzheimer's disease. Ongoing studies are also researching its effect on patients with Parkinson's Disease.

Alzheimer's disease continues to be a difficult clinical area to find successful treatment options. As discussed in our earlier pipeline reports, the approval of aducanumab, an anti-myeloid therapy was marred in controversy.

CONCLUSION

Bispecific antibodies hold great potential in various treatment conditions and in their growing market value. There are hundreds of trials in the pipeline with major players in the game such as Amgen, Genentech/Roche, Janssen/Johnson & Johnson, and Regeneron. BsAbs circumvent the need to administer two separate therapies and overcome challenges associated with dose-limiting toxicity, anti-drug antibody formation, or in cancer patients who have relapsed or became refractory to multiple systemic therapies. Since bsAbs can be administered in an outpatient setting and are viewed as possible alternatives to CAR-T cell therapies, they can have a significant impact on private plans.

Several innovative drug targets for diabetes, obesity, and Alzheimer's disease are being explored in the pipeline, which could alter future approaches to treatment for these highly prevalent conditions.

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