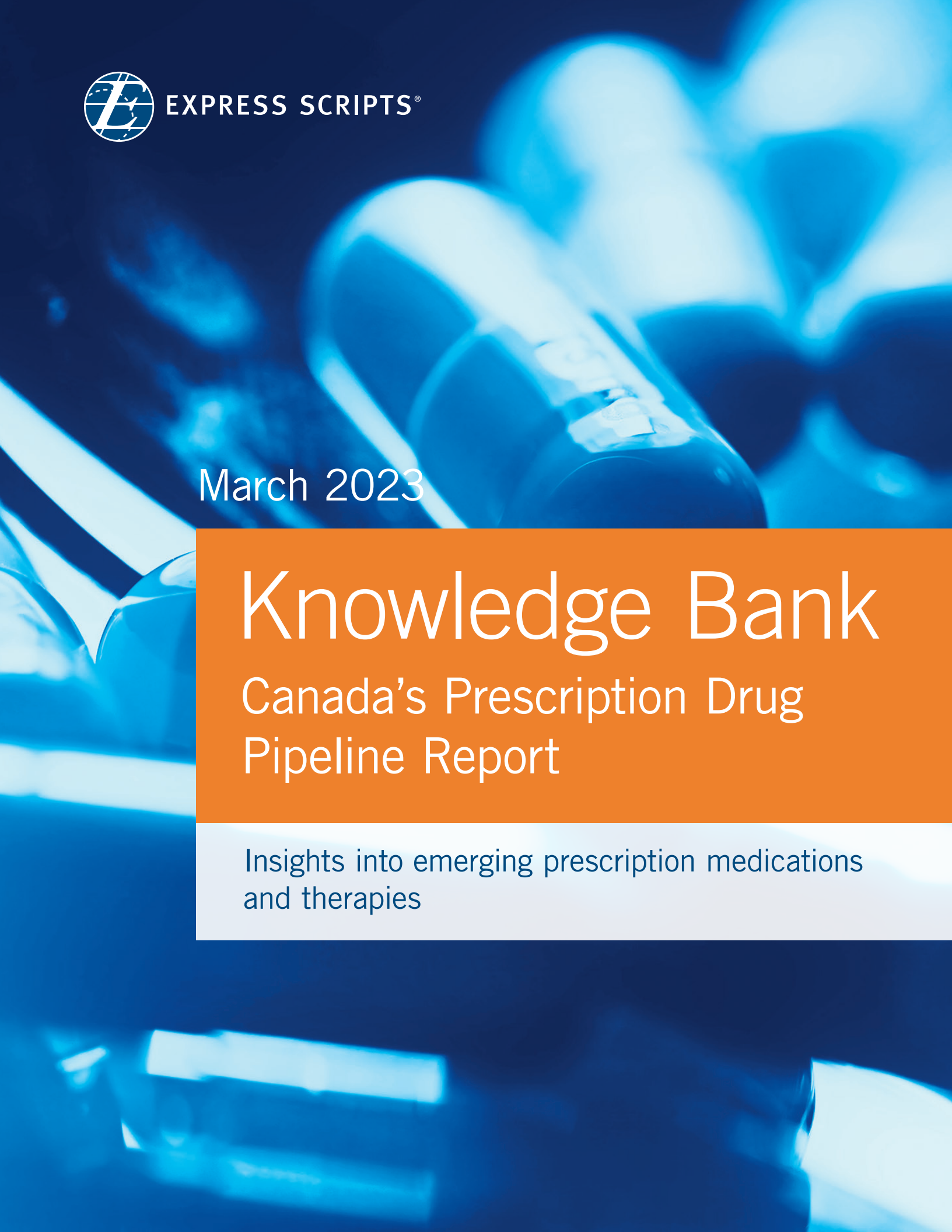

EXPRESS SCRIPTS®

March 2023

Knowledge Bank

Canada's Prescription Drug Pipeline Report

Insights into emerging prescription medications and therapies

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INTRODUCTION

Express Scripts Canada welcomes you to our first Knowledge Bank – Canada's Prescription Drug Pipeline Report – for 2023. In this issue, we follow the status of emerging treatments currently under review by Health Canada, and have the greatest impact on private plans.

As of March 1 2023, Health Canada is reviewing 81 drug submissions. We will continue to monitor biosimilar submissions and their potential to drive down costs for drug plans, as more jurisdictions adopt biosimilar switching initiatives.

This report also highlights several new drugs in oncology and rare diseases that have been recently submitted to Health Canada. These drugs are associated with high annual costs and if approved, may contribute to an increase in drug spend.

BIOSIMILARS

Table 1: Biosimilars under review by Health Canada

Common Name	Biologic Reference Drug	Therapeutic Area	Submission dates to Health Canada	Estimated Impact on Private Plans*
Ustekinumab	STELARA®	Immunosuppressants	2023-01	High
Filgrastim	NEUPOGEN®	Immunostimulants	2023-01	Low
Ranibizumab	LUCENTIS®	Ophthalmologicals	2022-12	High
Enoxaparin sodium	LOVENOX®	Antithrombotic agents	2022-09	Low
Aflibercept	EYLEA®	Ophthalmologicals	2022-05	High
Eculizumab	SOLIRIS®	Immunosuppressants	2022-07	Low
Bevacizumab	AVASTIN®	Antineoplastic agents	2022-03	Low
Pegfilgrastim†	NEULASTA®	Immunostimulants	2022-05	Low
Trastuzumab	HERCEPTIN®	Antineoplastic agents	2021-08	Low

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

† There are two pegfilgrastim biosimilar submissions under review.

Health Canada is currently reviewing ten biosimilars. Another filgrastim biosimilar was submitted earlier this year, along with the first biosimilar to STELARA® (ustekinumab). STELARA® is approved for several indications including plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. The drug has an estimated annual cost range from $20,000 to $32,100 for maintenance dosing depending on the indication used. A second ranibizumab biosimilar to LUCENTIS® was submitted for review in December 2022. LUCENTIS® has a high annual cost of up to $19,000 and is marketed to treat certain eye conditions leading to vision loss.[1]

With more provincial governments expanding biosimilar program initiatives as seen recently with Ontario,[2] the uptake of these biosimilars would offer cost-savings in drug spend.

[1] https://canjhealthtechnol.ca/index.php/cjht/article/view/SR0739/1125

[2] https://news.ontario.ca/en/release/1002611/ontario-expanding-safe-use-of-biosimilars

COMING SOON

Bispecific antibodies

In our previous pipeline report, we introduced an active area of drug research with the advent of bispecific antibodies (bsAbs) and their growing market value. BsAbs are antibodies that have been engineered to have two binding targets, and are being explored in various treatment applications, primarily in oncology.[3]

Glofitamab is a bsAb administered intravenously. It binds to CD20 found on malignant B cells and CD3 found on T cells (CD20xCD3). It is being investigated in people with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The drug was granted priority review by the FDA with a decision date set in July 2023. If approved, it will be the first fixed-duration, "off-the shelf" treatment available in this setting. It is also currently being reviewed by Health Canada under the Notice of Compliance with Conditions (NOC/c) Guidance. Drug submissions considered under this review pathway have a target of 200 calendar days[4] and thus, decision is expected to be released in 2023.

Table 2: Drug Submissions under Review by Health Canada Identified to have high Annual Costs

Drug Name	Therapeutic Area	Drug Format	Submission dates to Health Canada	Health Canada Anticipated Timing of Results‡	Estimated Cost (if available)
Glofitamab	Antineoplastic	Intravenous	2022-07	2023-03	N/A
Mirikizumab	Immunosuppressants	Subcutaneous	2022-09	2023-09	N/A
Nivolumab, Relatlimab	Antineoplastic agents	Intravenous	2022-09	2023-09	US $250,000
Efgartigimod alfa	Immunosuppressants	Intravenous	2022-11	2023-11	US $225,000
Setmelanotide	Antiobesity preparations	Subcutaneous	2022-11	2023-05	US $240,000 - $360,000
Teclistamab	Antineoplastic	Subcutaneous	2022-12	2023-07	US $355,000 - $395,000
Relugolix	Endocrine therapy	Tablet, Oral	2022-12	2023-12	US $28,000
Vutrisiran	Other nervous system drugs	Subcutaneous	2022-12	2023-12	US $463,500
Rimegepant	Analgesics	Tablet, Orally Disintegrating	2023-01	2024-01	N/A
Maralixibat	Bile and liver therapy	Solution, Oral	2023-01	2023-07	US $391,000

‡ Estimated decision dates for market authorization based on Health Canada's drug submission review target timelines found on the Health Canada website.

[3] https://www.frontiersin.org/articles/10.3389/fimmu.2021.626616/full

[4] https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/notice-aligned-reviews-health-canada-health-technology-assessment-organizations.html

We previously discussed the recent FDA approval of Janssen's TECVAYLI® (teclistamab) in October 2022. TECVAYLI® is a subcutaneous BCMAxCD3 bsAb indicated for the treatment of adult patients with R/R multiple myeloma who have received at least four prior lines of therapy. Since then, a drug submission was filed in December 2022 and it is undergoing Health Canada review under the NOC/c Guidance.

BsAb treatments offer flexibility in administration and improved accessibility compared to the complexities associated with cellular and gene therapies, which are generally the next line of treatment in R/R setting for blood cancers. These drug approvals could result in a shift in guidelines or standard of care from CAR-T cell therapies towards bsAbs.

Migraines

Calcitonin gene-related peptide (CGRP) receptor antagonists have changed the treatment landscape for chronic migraines. This new drug class has demonstrated excellent efficacy and tolerability in treatment-refractory migraines. Initially available as injectable therapies, progress in drug developments resulted in second-generation oral CGRP formulations, which have expanded their indications in both acute and preventative settings. Ubrogepant and atogepant are the first two oral CGRPs that received Health Canada approval late last year, indicated for acute treatment and preventative treatment, respectively. Meanwhile, NURTEC® (rimegepant) is marketed in the United States as an oral disintegrating tablet and is able to treat acute migraines, as well as prevent migraines for up to 48 hours. After obtaining both indications for rimegepant by May 2021, the company had reported net product revenue of US$194 million for Q2 2022, an increase of 57% from Q1 2022,[5] which carries a significant growth trajectory in the migraine market space. Health Canada just received a drug submission for its review in January 2023.

Oncology

A Health Canada submission review for relugolix has been filed on December 2022 with an expected decision date by Q4 2023. ORGOVYX® (relugolix) was approved by the FDA in December 2020 and is the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the treatment of adult patients with advanced prostate cancer. Existing GnRH analogues are available as subcutaneous formulations only.

ORGOVYX® has a much higher monthly cost of approximately US$2,300 in comparison to LUPRON DEPOT® (leuprolide), a GnRH analog priced at CAD$400 per month.[6] Long-acting injectable formulations would still be preferential for adherence and convenience, especially in cancer treatment, but relugolix could be an alternative option to patients who are needle-averse.

[5] https://pharma3.globaldata.com/News/biohaven-reports-second-quarter-2022-financial-results-and-reports-recent-business-developments-9909274

[6] https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10149Enzalutamidenm-CRPC_fnEGR_EC_NOREDACT-ABBREV_Post_26Mar2019_final.pdf

In unresectable or metastatic melanoma, a first-in-class, fixed-dose dual immunotherapy was approved by the FDA in March 2022. Bristol Myers Squibb's OPDUALAG® combines nivolumab (anti-PD1), and relatlimab (anti-LAG-3) administered as one single infusion. It has an estimated annual cost of more than US$486,000. It targets two inhibitory immune checkpoints (PD-1 and LAG-3) resulting in greater T-cell activation against tumour cells. Standard treatment in this setting includes a combination therapy of nivolumab and ipilimumab administered separately, which has an annual cost of approximately US$250,000, slightly more than half that of OPDUALAG®, but may be associated with more serious side effects.[7] Health Canada has received a submission review for this therapy in September 2022 with an expected decision date by Q3 2023.

Ulcerative Colitis

Newer treatments for plaque psoriasis have been focused on targeting cytokine IL-23, including SKYRIZI®, ILUMYA®, TREMFYA®, and STELARA®. In this competitive space, Eli Lilly decided not to pursue its plaque psoriasis program for mirikizumab, an anti-IL-23, despite establishing efficacy and superiority to a marketed anti-IL-17 biologic, secukinumab back in 2019. Instead, Lilly's focused its efforts on establishing its place in ulcerative colitis and Crohn's disease therapeutics market.

Mirikizumab is currently under evaluation by the FDA for ulcerative colitis and is expected to be released in May 2023, while its Crohn's disease launch is expected in 2025. If approved, mirikizumab will become first-in-class for ulcerative colitis. Lilly also submitted to Health Canada for a review of mirikizumab and awaiting marketing authorization by Q3 2023.

Rare Diseases

Alnylam submitted a drug review to Health Canada for vutrisiran in December 2022. AMVUTTRA® (vutrisiran) was approved by the FDA on June 2022. It is a subcutaneous injection administered every three months for the treatment of hereditary transthyretin (hATTR) amyloidosis with polyneuropathy. Hereditary ATTR is a rare, progressive, debilitating, fatal condition where mutations in the TTR gene result in misfolded protein aggregates, leading to organ and tissue damage. Most common systems affected are the nerves (polyneuropathy) and heart (cardiomyopathy).[8] There are two disease modifying therapies currently in the market, ONPATTRO® (patisiran) administered via intravenous infusion every three weeks, and TEGSEDI® (inotersen) administered once per week via a subcutaneous injection. These two treatments have high annual cost ranges from $420,000 to $680,000 per patient.[9, 10] AMVUTTRA® is a transthyretin-directed small interfering RNA treatment that inhibits the expression of the mutated TTR gene and thus lowers levels of TTR protein in the blood. Alnylam revealed that the annual list price of AMVUTTRA® will be approximately US$463,500, on par with ONPATTRO®.

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[7] https://www.nejm.org/doi/full/10.1056/nejmoa2109970

[8] https://pubmed.ncbi.nlm.nih.gov/33631091/

[9] https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0598-onpattro-pharmacoeconomic-review-report.pdf

[10] https://www.cadth.ca/sites/default/files/cdr/complete/SR0603%20Tegsedi%20-%20Final%20CDEC%20Recommendation%20December%2020%2C%202019%20for%20posting.pdf

Myasthenia gravis (MG) is a rare autoimmune neuromuscular condition that is experiencing great advancements in drug development. For decades, available treatments involved conventional long-term immunosuppressive therapies and monoclonal antibodies for refractory disease. VYVGART® (efgartigimod alfa), a first-of-its-kind treatment that was submitted to Health Canada for review on November 2022. The drug had already received FDA approval for generalized MG since December 2021.

From our previous pipeline reports, we've discussed that immunotherapies in refractory disease such as SOLIRIS® (eculizumab) are directed mainly at suppressing the immune system, and comes at a high annual cost of over $700,000 per patient.[11] On the other hand, VYVGART® specifically targets and facilitates the degradation of circulating anti acetylcholine receptor antibodies which are largely responsible for the clinical development of the disease.[12] Average annual cost for VYVGART® is estimated to be US$225,000 depending on weight and number of treatments required by the patient.

We continue to follow developments in anti-obesity medications since the Health Canada approval of WEGOVY® (semaglutide) and FDA submission of MOUNJARO® (tirzepatide) for the treatment of adults with obesity or overweight with weight-related comorbidities.

A potential treatment for monogenic or syndromic obesity associated with certain ultra-rare genetic conditions called setmelanotide, was submitted to Health Canada under priority review in November 2022. Health Canada drug reviews assigned with a priority review have a shortened review target of 180 calendar days.[4] Setmelanotide was granted orphan disease designation, breakthrough therapy designation, and later approved by the FDA for obesity management related to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome (BBS) in patients 6 years and over. Patients with these conditions have normal birth weights but experience progressive weight gain due to genetic defects that impair their appetite, satiety and metabolism.[13] It can be administered by the patient as a subcutaneous injection, with an annual cost of about US$240,000 to $360,000.

Lastly, another drug on our radar is Mirum's LIVMARLI® (maralixibat) which was approved by the FDA in September 2021. LIVMARLI® is the first and only treatment approved for cholestatic pruritus in patients one year and older with Alagille syndrome (ALGS). ALGS is a rare genetic disease that causes bile duct abnormalities resulting to bile accumulation in the liver. Bile build-up clinically manifests in infants as jaundice, xanthomas (fat deposits under the skin), as well as intense, incessant, debilitating itch (cholestatic pruritus).[14] Maralixibat is a once-daily, orally administered medication and has an estimated annual cost of US$391,000. It was submitted to Health Canada under the priority review policy in January 2023.

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[11] https://www.cadth.ca/sites/default/files/cdr/complete/SR0605%20Soliris%20MG%20-%20CDEC%20Final%20Recommendation%20October%2021%2C%202020_for%20posting.pdf

[12] https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-myasthenia-gravis

[13] https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-weight-management-people-certain-rare-genetic-conditions

[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6167076/?report=classic

CONCLUSION

Research and drug development in oncology and rare diseases remain to be a key focus for the pharmaceutical industry. New modalities with bispecific antibodies, dual immunotherapies, and shifts in self-administered therapies are on the rise, even in relapsed and refractory disease settings, which could introduce new costs for private payers.

The growing number of these high-cost specialty medications will require cost-effective strategies to ensure their appropriate use and the sustainability of health benefits plans.

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