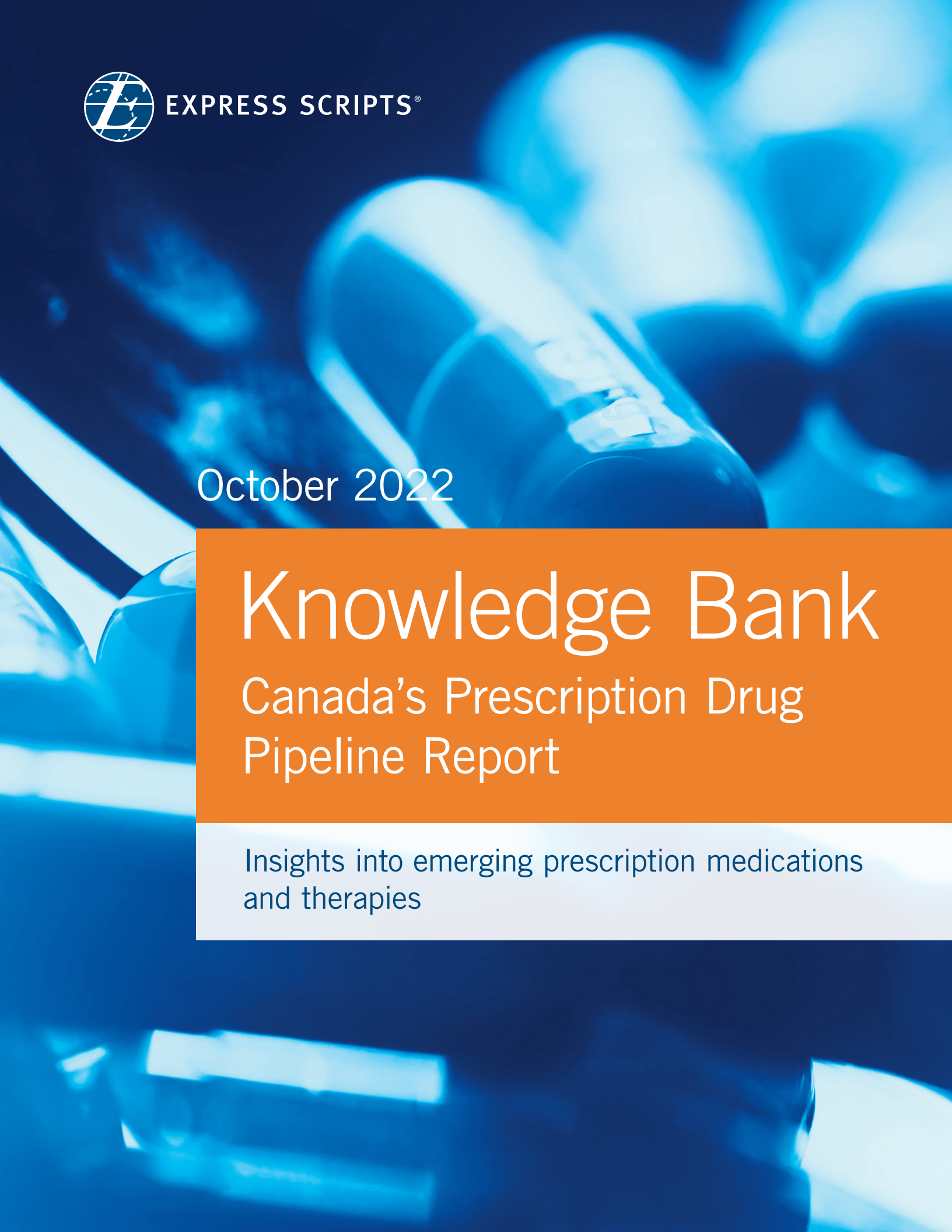

EXPRESS SCRIPTS®

October 2022

Knowledge Bank

Canada's Prescription Drug Pipeline Report

Insights into emerging prescription medications and therapies

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INTRODUCTION

Welcome to the October 2022 edition of Knowledge Bank – Express Scripts Canada's Drug Pipeline Report. We continue to focus on emerging treatments in Canada that will have the greatest impact on private plans.

We present multiple updates from previous pipeline reports as part of our ongoing surveillance, including a newly approved monoclonal antibody for asthma, a highly anticipated Alzheimer's treatment, and the Health Canada submission of a new oral psoriasis treatment that could compete in the biologics space. We also continue to follow the status and approval of biosimilars under review by Health Canada.

In addition, this report highlights treatment developments in neuromuscular disorders and rare disease forms that can offer potential survival benefits for patients.

Rounding out the updates, we look at the shift of treatments from subcutaneous injections to oral routes of administration on two major inflammatory conditions: ulcerative colitis and psoriasis.

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®	Opthalmologicals	2022-05	High
Bevacizumab	AVASTIN®	Antineoplastic agents	2022-03	Low
Eculizumab	SOLIRIS®	Immunosuppressants	2022-07	Low
Enoxaparin sodium	LOVENOX®	Antithrombotic agents	2021-12	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 brand, and annual drug cost.

In an update from previous reports, Health Canada is reviewing 7 biosimilars. Since the last quarterly report, RYMTI® has now been approved and will be the third biosimilar alternative for etanercept. MYXREDLIN® is the biosimilar for NOVOLIN®GE TORONTO but will be indicated solely for use by intravenous injection under close medical supervision. A new addition to the list is eculizumab. Eculizumab is used to treat rare diseases and has a substantial annual cost of approximately $500-700,000.

Aducanumab in Alzheimer's Disease

We were anticipating the entry of Biogen's new agent for Alzheimer's disease to the Canadian market since our first Pipeline report in 2021. However, this summer, Biogen announced their withdrawal of aducanumab from regulatory review after Health Canada completed their assessment and found that clinical efficacy and safety data provided did not support aducanumab's clinical benefit as a disease modifying treatment for Alzheimer's disease in adults.[1]

Despite this withdrawl, the potential impact of Alzheimer's disease remains substantial. A recent CADTH report[2] estimated that the annual cost of dementia care to the Canadian health care system will double by 2031. With similar therapies like donanemab and lecanemab being accepted for priority review by the FDA this year, it is expected the drug development and research in this area to continue.

[1] Health Canada Regulatory Decision Summary of Aduhelm. Drug and Health Product Submissions Under Review (SUR): New drug submissions completed. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detailTwo.php?lang=en&linkID=RDS00966

[2] Varette, O., et al. Understanding the Portrait of Dementia Care in Canada: A CADTH Panel of Experts. Can J Health Technol. 2022.412. 10 Aug 2022, doi.org/10.51731/cjht.2022.412

Elacestrant in Breast Cancer

There has been a growing shift in cancer treatment to oral therapy from traditional hospital-administered therapies. In our last pipeline report, we alluded to investigational oral selective estrogen receptor degraders (SERDs) underway for the treatment of hormone receptor positive metastatic breast cancer. Elacestrant becomes the first oral SERD to seek FDA approval, demonstrating positive results in their pivotal Phase III EMERALD study,[3] showing that elacestrant was associated with a statistically significantly prolonged progression-free survival compared with the standard-of-care endocrine therapy in this patient population.

Gene Therapy in Beta-Thalassemia

After its initial rejection in 2021 from the FDA, ZYNTEGLO® (betibeglogene automcel) by Bluebird Bio finally received approval on Aug 17, 2022 for the treatment of beta-thalassemia in adult and pediatric patients who require regular red blood cell transfusions. Beta-thalassemia is an inherited blood disorder caused by a mutation in a gene that codes for beta globin protein, an important component in functional hemoglobin production. It becomes the first cell-based gene therapy for treatment in this population, available as a single dose infusion. It involves using the patient's own stem cells which have been mobilized and engineered outside the body to contain the functioning gene, and transplanting these cells back to the body.[4] It currently has a listed price of $2.8M per patient in the United States (U.S.). There is no recent Health Canada submission under review for this drug thus far, but with the significant upfront costs to emerging gene therapies like ZYNTEGLO®, negotiations on pricing and reimbursement models with multi-stakeholders are necessary.

Deucravacitinib in Psoriasis

Lastly, another medication we discussed from our previous pipeline report is Bristol Myers Squibb's SOTYKTU® (deucravacitinib). It was approved by the FDA on Sept 9, 2022 and the company has submitted to Health Canada earlier this year and later to CADTH for review. Deucravacitinib is a first-in-class, oral, tyrosine kinase 2 (TYK2) inhibitor for the treatment of moderate to severe plaque psoriasis. It has outperformed another oral treatment OTEZLA® (apremilast), showing superior efficacy and a more sustained response in its pivotal Phase 3 trials POETYK PSO-1 and POETYK PSO-2. It will be competing against other biologic drugs such as HUMIRA® (adalimumab) and ENBREL® (etanercept), and will offer patients the convenience and ease of a once-daily oral tablet which could soon change the standard of care for those who failed topical and conventional therapies.

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[3] Bidard, F., et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, JCO2200338. 18 May. 2022, doi:10.1200/JCO.22.00338

[4] Beaudoin, F., et al. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, June 2, 2022. https://icer.org/beta-thalassemia-2022/#timeline

COMING SOON

Asthma

Health Canada approved TEZSPIRE® (tezepelumab) on July 28, 2022 for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. This drug is a first-in-class human monoclonal antibody that specifically blocks thymic stromal lymphopoietin (TSLP), a key epithelial cytokine responsible in initiating the overreactive immune response associated with severe asthma. In the key study trials, tezepelumab resulted in statistically significant lowered annualized rate of asthma exacerbations than placebo. It is the first and only biologic approved for severe asthma without phenotypic or biomarker limitations unlike its comparators DUPIXENT® (dupilumab) and XOLAIR® (omalizumab). Although Canadian pricing is not yet available, estimated annual cost in the U.S. is around $47,000, posing a potential increase in spend due to lack of criteria restrictions in its use in severe asthma.

Neuromuscular Disorders

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disorder affecting motor neurons. Disease modifying therapies are very limited and lack meaningful survival benefit. A new investigational oral therapy, masitinib, by AB Science could offer a substantial survival benefit in combination with RILUTEK® (riluzole) when initiated at earlier stages of the disease. Masitinib has received orphan drug designation for ALS from both the EMA and FDA, and has now been accepted for review by Health Canada under the notice of compliance with conditions (NOC/c) policy, as part of an expedited review process. If approved, this add-on treatment could provide hope for patients with ALS in extending survival for a median of 25 months compared to riluzole alone.

Tofersen is another treatment in the ALS drug pipeline but for rare genetic form called superoxide dismutase 1 ALS (SOD1-ALS). It has recently received priority review from the FDA despite its Phase III VALOR study not meeting its primary endpoints. Tofersen will be administered as monthly intrathecal injections, and if granted approval, it would be the first treatment to target this particular form of ALS. At the time of this report, there is no submission under review at Health Canada.

Myasthenia gravis (MG) is a rare autoimmune neuromuscular disorder, where the patient's own immune system attacks the acetylcholine receptor sites located in the junction between motor nerves and muscles, resulting in muscle weakness and fatigue. There have been several emerging immunotherapies for generalized MG soon after the Health Canada approval of SOLIRIS® (eculizumab) in 2018. One on the horizon is ULTOMIRIS® (ravulizumab) by Alexion/AstraZeneca has gained FDA approval. It is a new long-acting C5 complement inhibitor, requiring less frequent infusions at every 8 weeks compared to every 2 weeks with eculizumab. At the time of this report, there is no submission under review at Health Canada for ravulizumab. Other pipeline therapies of interest include zilucoplan and batoclimab, which could potentially offer subcutaneous injections for self-administration.

Rare Diseases

FDA approved XENPOZYME® (olipudase alfa), the first treatment for the extremely rare progressive genetic disease acid sphingomyelinase deficiency (ASMD) that causes premature death in both children and adults. The FDA granted the drug with priority review and orphan drug designations for ASMD. XENPOZYME® is an enzyme replacement therapy designed to replace the defective ASM protein, allowing for the proper breakdown of lipid sphingomyelin and prevent its accumulation in the liver, spleen, lung, and brain. It will be administered every 2 weeks with a U.S. list price of about $7,142 per vial. Since XENPOZYME® has already been approved in Japan and European markets earlier this year, it will likely make its waves to Canada soon. At the time of this report, there is no submission under review at Health Canada.

Dermatology

Generalized pustular psoriasis (GPP) is a rare and extreme form of psoriasis that causes itchy and sterile pus-filled blisters over large surface areas of the body, including inside the mouth. Acute widespread flare-ups can be life-threatening, requiring emergency medical care. SPEVIGO® (spesolimab) was recently approved by the FDA as the first treatment option of GPP flares in adults, which may result in a huge impact on the standard clinical practice in managing these patients. At the time of this report, there is no submission under review at Health Canada.

FURTHER DOWN THE LINE

Ulcerative Colitis

Many experimental agents for the treatment of moderate to severe ulcerative colitis (UC) are making their way in the pipeline, with varying mechanisms of action and routes of administration. Of note are two agents, obefazimod and cobitolimod with promising results.

Obefazimod is a first-in-class oral therapy that upregulates micro-RNA-124 which naturally inhibits the production of inflammatory mediators implicated in various autoimmune inflammatory diseases. Patients on obefazimod who were documented as refractory to biologics (e.g. tumor necrosis factor inhibitors (TNFs), vedolizumab), and/or JAK inhibitors, achieved statistically significant clinical response and remission compared to placebo as early as 8 weeks of therapy. It is important to note that the majority of patients (71%) had severe baseline disease activity.[5] The company Abivax is also looking into other indications of obefazimod, namely rheumatoid arthritis, Crohn's disease, and COVID-19 infections.

On the other hand, cobitolimod also has a novel mechanism of action with an interesting route of administration being marketed as a locally administered rectal enema. It is a toll-like receptor 9 (TLR9) agonist that triggers certain anti-inflammatory cytokines to be produced to reduce inflammation and promote epithelial healing. Efficacy and safety results of its pivotal Phase III CONCLUDE study are still not fully available; however, its unique administration route may limit systemic absorption and thus provide a more favorable side effect profile than the currently available systemic or biologic agents in the market.

Psoriasis

Innovations in psoriasis treatment shows no signs of stopping. In this quarter, another upcoming oral therapy by Can-Fite BioPharma for the treatment of moderate to severe plaque psoriasis is planning to enter the U.S. and European market. Piclidenoson is a first-in-class, oral, A3 adenosine receptor agonist (A3AR) which results in the inhibition of interleukins 17 and 23, two inflammatory cytokines implicated in psoriasis. In their pivotal Phase III COMFORT trial, piclidenoson demonstrated comparable efficacy to apremilast (OTEZLA®) specifically in patients with severe disease, had a better tolerability profile, and was superior in improving quality of life measures to apremilast as measured in Psoriasis Disability Index scores. Deucravacitinib's recent FDA approval and efficacy results mentioned earlier may overshadow piclidenoson's market success if it is granted approval in the future.

[5] Vermeire, Severine et al. ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2b, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension. The lancet. Gastroenterology & hepatology, S2468-1253(22)00233-3. 5 Sep. 2022, doi:10.1016/S2468-1253(22)00233-3

Geographic Atrophy

Geographic atrophy (GA) is part of the late-stage disease of dry age-related macular degeneration (AMD). Patients with GA develop lesions that causes irreversible retinal damage which can progress to blindness over time. Apellis Pharmaceuticals' pegcetacoplan has received priority review designation from the FDA for GA, and is the only treatment currently being reviewed. It is a targeted C3 therapy which regulates the overactivation of the complement cascade as part of the body's inflammatory response. Monthly and bi-monthly intravitreal injections showed clinically meaningful reduction in disease progression across three large Phase 2 and Phase 3 studies (DERBY, OAKS, and FILLY). Approval of pegcetacoplan could be a breakthrough treatment in patients at high risk of significant vision loss.

CONCLUSION

Several treatments presented in this pipeline report are for disease conditions that have not seen advancements in years (e.g., Alzheimer's Disease, neuromuscular, and genetic/blood disorders) and could offer patients improved survival outcomes and quality of life benefits. As the drugs highlighted are disease modifying therapies, they are expected to have significant financial impact on private plans despite affecting a small number of claimants.

Innovations in drug development are now shifting towards convenient, oral route of administration, especially in cancer and inflammatory conditions where intravenous or subcutaneous routes are most prevalent. Both of these conditions were identified as part of the Top 10 Therapeutic Classes based on overall drug spend from ESC's 2022 Drug Trend Report. The rise of new oral therapies and their associated costs will shape future drug trend.

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