Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the January to March 2016 DEC Meetings

The Drug Evaluation Committee (DEC) of Express Scripts Canada conducts monthly reviews of all new drugs receiving their Notice of Compliance from Health Canada, to ascertain their place in therapy and their possible impact on the private payer sector. The prices quoted in this document are approximations for general information purposes only, and are not intended, nor should they be relied upon, for purposes of any actual claims adjudication or reimbursement. This publication, describing new drugs of significance, is provided to our customers on a quarterly basis as a value-added service. We hope that you will find this Health Newsflash informative, timely, and useful.

NEW DRUGS

Bydureon® (exenatide LAR)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02448610 – 2mg/dose	AstraZeneca Canada Inc.	68:20.06 – Incretin mimetics

Indication(s)

Bydureon is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus:

- as monotherapy, in patients for whom metformin is inappropriate due to contraindications or intolerance
- in combination with metformin, when metformin used alone does not provide adequate glycemic control
- in combination with a sulfonylurea, when the sulfonylurea used alone does not provide adequate glycemic control
- in combination with metformin and a sulfonylurea, when dual therapy with these two agents does not provide adequate glycemic control.

Dose

Bydureon 2 mg should be administered once every seven days (weekly). The dose can be administered at any time of day, with or without meals.

Therapeutic Alternatives

Byetta (exenatide), Victoza (liraglutide), Eperzan (albiglutide), Trulicity (dulaglutide)

Clinical Notes

Once weekly exenatide long-acting release (LAR) (Bydureon) is a subcutaneously injectable extended-release formulation glucagon-like peptide 1 (GLP-1) receptor agonist developed as an extension to the approved Byetta immediate-release, twice-daily (BID) product line. In this LAR formulation, the exenatide molecule is dispersed in microspheres. Following subcutaneous injection, drug is slowly released from these microspheres.

When compared to twice-daily exenatide (Byetta) (DURATION-1), Bydureon demonstrated superior blood glucose control based on average reduction in HbA1c and proportion of patients achieving the Canadian Diabetes Association (CDA) endorsed general HbA1c target of ≤ 7.0%. Bydureon was compared to Victoza (liraglutide) in a head-to-head clinical trial (DURATION-6) with liraglutide showing superior blood glucose lowering efficacy in terms of HbA1c reduction. There are no comparisons between Bydureon and the other approved once-weekly GLP-1 receptor agonists, Eperzan (albiglutide) and Trulicity (dulaglutide).

Place in Therapy

Bydureon is the third once-weekly administered GLP-1 receptor agonist approved in Canada. Its full place in therapy is yet to be established.

Comparative Pricing

Drug	Estimated Annual Cost
Bydureon	$2,700
Byetta	$1,800
Victoza	$2,000 - $3,100
Trulicity	$2,700

Impact/Plan Management Suggestions

Minimal impact – due to cost shift from daily use GLP-1 receptor agonists. Bydureon may be managed similar to other GLP-1 receptor agonists.

Cotellic™ (cobimetinib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02452340 – 20mg	Hoffmann La Roche Ltd.	10:00.00 – Antineoplastic agents

Indication(s)

Cotellic (cobimetinib) is indicated for use in combination with vemurafenib (Zelboraf) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Dose

The recommended dose is 60 mg (three 20 mg tablets) once daily. Cotellic is taken on a 28-day cycle, with 60mg taken once a day for 21 consecutive days (days 1 to 21 – treatment period); followed by a 7-day break in treatment (days 22 to 28 – treatment break). Each subsequent Cotellic treatment cycle should start after the 7-day treatment break has elapsed.

Therapeutic Alternatives

Mekinist (trametinib) used in combination with Tafinlar (dabrafinib).

Clinical Notes

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK), extracellular signal regulated kinase 1 (MEK1), and MEK2. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. V600 BRAF mutations, including V600E, result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. When combined with vemurafenib, two kinases are targeted in the RAS/RAF/MEK/ERK pathway, thereby reducing the likelihood of resistance developing in the cancer cells.

The efficacy and safety of combination cobimetinib plus vemurafenib treatment was compared to vemurafenib monotherapy in a randomized phase 3 trial (coBRIM) of patients with BRAFV600 mutation positive metastatic melanoma. The coBRIM trial met all its endpoints, demonstrating statistically and clinically significant benefits including: median progression free survival, median overall survival, overall response rate, complete response, and duration of response. Most patients showed a response to therapy within eight weeks.

Place in Therapy

Cotellic is indicated in adults for treatment of unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with vemurafenib. Progression-free survival was significantly improved with addition of Cotellic to vemurafenib compared with addition of placebo during a randomized study. Cotellic is not indicated in patients with wild-type BRAF melanoma.

Comparative Pricing

Drug Regimen	Estimated annual cost
Cotellic + Zelboraf	$209,000
Mekinist + Tafinlar	$209,000

Impact/Plan Management Suggestions

Minimal impact – cost shift from alternative treatment – Mekinist + Tafinlar – both of which are similarly priced high cost therapies. Manage with Prior Authorization to ensure appropriate utilization.

Genvoya™ (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02449498 – 150/150/200/10mg	Gilead Sciences Canada Inc.	08:18.08 – HIV Antiretrovirals

Indication(s)

Genvoya is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (and weighing > 35 kg) and with no known mutations associated with resistance to the individual components of Genvoya.

Dose

The dose of Genvoya is one tablet taken orally once daily with food.

Therapeutic Alternatives

An antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (cobicistat or ritonavir). The following regimens are considered to be recommended regimens for antiretroviral-naive patients:

Integrase Strand Transfer Inhibitor-Based Regimens:

1. Triumeq™ (Dolutegravir/abacavir/lamivudine) – only for patients who are HLA-B*5701 negative
2. Tivicay® + Truvada® (Dolutegravir plus tenofovir disoproxil fumarate [tenofovir]/emtricitabine)
3. Stribild® (Elvitegravir/cobicistat/tenofovir/emtricitabine) – only for patients with intact kidney function
4. Isentress® + Truvada® (Raltegravir plus tenofovir/emtricitabine)

Protease Inhibitor-Based Regimen:

- Prezista® + Norvir® + Truvada® (Darunavir/ritonavir plus tenofovir/emtricitabine)

Clinical Notes

Genvoya is a one tablet daily regimen for treating HIV-1 infection. It is similar to Stribild® with the only difference being tenofovir disoproxil fumarate being replaced with tenofovir alafenamide. Tenofovir alafenamide (TAF) is an oral prodrug of tenofovir (TFV). TAF is converted to TFV and then to TFV-diphosphate intracellularly, where it exerts its activity as a reverse transcriptase inhibitor. Unlike tenofovir disoproxil fumarate (TDF), which readily converts to TFV in plasma after oral absorption, TAF remains stable in plasma resulting in lower plasma and higher intracellular TFV concentrations. When orally administered TAF (10 mg) and TDF (300 mg) were compared, plasma TFV concentrations were 90% lower in participants who received TAF than in those who received TDF. Because of the lower plasma TFV concentration, the potential for adverse kidney and bone effects is less with TAF than with TDF. Clinical trials have confirmed that this drug was non-inferior to Stribild with respect to antiretroviral efficacy. It has been shown to be safe in individuals with mild to moderate kidney dysfunction.

Place in Therapy

Based on efficacy and safety data from phase 3 randomized clinical trials, Genvoya (EVG/c/FTC/TAF) has been added by the Panel on Antiretroviral Guidelines for Adults and Adolescents of the U.S. Department of Health and Human Services (whose recommendations are followed by Health Canada) as one of the Recommended Initial Regimens for ART-naive adults and adolescents with estimated creatinine clearance ≥ 30 mL/min.

Pricing

Drug	Estimated Annual Cost
Genvoya	$18,000
Stribild	$18,000
Triumeq	$16,000

Impact/Plan Management Suggestions

Minimal impact – potential cost shift from similar priced regimens.

Grastofil™ (filgrastim)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02441489 – 300mcg/0.5ml PFS	Apotex Inc.	20:16.00 – Hematopoietic Agents

Indication(s)

Grastofil™ (filgrastim) is indicated for the following:

1. Cancer Patients Receiving Myelosuppressive Chemotherapy

Grastofil (filgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs. Grastofil is indicated in adult and pediatric patients with cancer receiving myelosuppressive chemotherapy.

A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy and twice per week during Grastofil therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, filgrastim therapy was discontinued when the ANC was > 10 × 109/L after expected chemotherapy-induced nadir.

2. Patients with Acute Myeloid Leukemia

Grastofil is indicated for the reduction in the duration of neutropenia, fever, antibiotic use and hospitalization, following induction and consolidation treatment for acute myeloid leukemia.

3. Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

Grastofil is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g. febrile neutropenia, in patients undergoing myeloablative therapy followed by bone marrow transplantation.

A CBC and platelet count should be obtained at a minimum of 3 times per week following marrow infusion to monitor marrow reconstitution.

4. Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

Grastofil is indicated for the mobilization of autologous peripheral blood progenitor cells in order to accelerate haematopoietic recovery by infusion of such cells, supported by filgrastim after myelosuppressive or myeloablative chemotherapy.

5. Patients with Severe Chronic Neutropenia (SCN)

Grastofil is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic or idiopathic neutropenia.

6. Patients with HIV Infection

Grastofil is indicated in patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal ANC (e.g. between 2 × 109 and 10 × 109/L).

Grastofil therapy reduces the clinical sequelae associated with neutropenia (e.g. bacterial infections) and increases the ability to deliver myelosuppressive medications used for the treatment of HIV and its associated complications. It is recommended that complete blood counts and platelet counts be monitored at regular intervals (e.g. initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during Grastofil therapy.

These are the same indications as Neupogen®.

Dose

Cancer Patients Receiving Myelosuppressive Chemotherapy

The recommended starting dose of Grastofil in adult patients is 5 µg/kg/day, administered as a single daily injection by subcutaneous bolus injection, by short intravenous infusion (15 to 30 minutes), or by continuous subcutaneous or continuous intravenous infusion.

The recommended dose in pediatric oncology patients is 5 µg/kg/day administered subcutaneously.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

The recommended dose of Grastofil following bone marrow transplant is 10 µg/kg/day given as an intravenous infusion of 4 to 24 hours, or a continuous 24-hour subcutaneous infusion.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

The recommended dose of Grastofil for PBPC mobilization is 10 µg/kg/day given as a single daily subcutaneous injection or a continuous 24-hour infusion.

Patients with HIV Infection

The recommended starting dose of Grastofil is 1 µg/kg/day or 300 µg 3 times per week by subcutaneous injection until a normal neutrophil count is reached and can be maintained (ANC $\geq 2 \times 109/L$). Dose adjustments may be necessary as determined by the patient's ANC to maintain the ANC between $2 \times 109/L$ and $10 \times 109/L$.

Patients with Severe Chronic Neutropenia

Starting Dose:
Congenital Neutropenia: The recommended daily starting dose is 12 µg/kg subcutaneously (single or divided dose).
Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 µg/kg subcutaneously (single or divided dose).

Therapeutic Alternatives

Neupogen (filgrastim); Neulasta (pegfilgrastim)

Clinical Notes

Grastofil (filgrastim) is a subsequent entry biologic product to the reference product Neupogen® (filgrastim). Grastofil consists of a recombinant methionyl human granulocyte-colony stimulating factor (r-metHuG-CSF) that binds with high affinity to the G-CSF receptor (G-CSFR). The biosimilarity between Grastofil™ and Neupogen® was established in accordance with Health Canada's *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).*

Cytotoxic chemotherapy suppresses the hematopoietic system causing profound and sometimes prolonged neutropenia. Chemotherapy-induced neutropenia is the major dose-limiting toxicity of systemic cancer chemotherapy. It may result in hospitalisation for treatment of fever or cause potentially fatal infection. Such complications of chemotherapy treatment often result in dose reduction or treatment delay which may compromise clinical outcomes. Risk factors for cytotoxic chemotherapy-induced neutropenia are: advanced age, poor performance status, poor nutritional status and low baseline and first cycle nadir blood cell count along with high chemotherapy dose intensity. Some chemotherapy regimens are more myelosuppressive than others. High cyclophosphamide dose, etoposide and high anthracycline doses have been identified as significant predictors for severe neutropenia.

Prophylactic antibacterial, antifungal, and antiviral agents have been administered to prevent the development of infection as a complication of neutropenia. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are used to reduce the duration and degree of neutropenia. G-CSF increases the proliferation and differentiation of neutrophils from progenitor cells, induces maturation and enhances the survival and function of mature neutrophils.

The active substance in Grastofil, filgrastim, is very similar to a human protein called granulocyte colony stimulating factor (G-CSF). Filgrastim acts in the same way as naturally produced G-CSF by encouraging the bone marrow to produce more white blood cells. The filgrastim in Grastofil is produced by a method known as 'recombinant DNA technology': it is made by bacteria into which a gene (DNA) has been introduced that makes them able to produce filgrastim.

Place in Therapy

Grastofil will become the first SEB for Neupogen®, available at a significant discount to the price of the reference brand.

Pricing

Drug	Estimated unit cost
Grastofil™	$155 (300µg)
Neupogen®	$185 (300µg) $295 (480µg)

Impact/Plan Management Suggestions

Minimal impact – potential cost savings.

Kyprolis™ (carfilzomib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02451034 – 60mg/vial	Bristol-Myers Squibb Canada	10:00.00 – Antineoplastic agents

Indication(s)

Kyprolis (carfilzomib) in combination with lenalidomide and dexamethasone is indicated for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy.

Dose

Kyprolis is administered by intravenous (IV) infusion over 10 minutes, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28) for the first 12 treatment cycles. Each 28-day period is considered one treatment cycle. For cycles 13 onwards, Kyprolis is administered on Days 1, 2, 15 and 16 followed by the 12-day rest period (i.e., the Days 8 and 9 Kyprolis doses are omitted).

Kyprolis is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, the dose should be escalated to a target dose of 27 mg/m^2 on Day 8 of Cycle 1. Treatment may be continued until disease progression or until unacceptable toxicity occurs.

The dose is calculated using the patient's baseline body surface area (BSA). Patients with a body surface area greater than 2.2m^2 should receive a dose based upon a body surface area of 2.2m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

In combination with Kyprolis, lenalidomide is administered as 25 mg orally on Days 1–21 and dexamethasone is administered as 40 mg orally/intravenously on Days 1, 8, 15, and 22 of the 28 day cycles.

Therapeutic Alternatives

Velcade (bortezomib)

Clinical Notes

Multiple myeloma (MM) is the second most prevalent blood cancer after non-Hodgkin's lymphoma. According to the 2011 Canadian Cancer Statistics report there are approximately 7,000 Canadians living with myeloma. It is estimated that in 2011, 2,300 new cases of myeloma will be diagnosed in Canada, and there will be 1,370 myeloma deaths. In the period 1997-2006, the annual percentage change in mortality rate amongst men was -1.6% and in women -0.4%. Myeloma makes up 1.3 percent of all new cancer cases in Canada and 1.8 percent of all cancer deaths. Men outnumber women amongst both newly diagnosed cases (1,300 men and 1000 women) and deaths (730 men and 640 women). Relatively little conclusive research has been conducted on the epidemiology of myeloma in Canada. MM is a disease of older adults. The average age at diagnosis is 62 years for men and 61 years for women, and only 4% of cases are diagnosed in individuals under the age of 45.

The clinical presentation is characterized by anaemia, bone disease, impaired renal function, hypercalcaemia, recurrent infections, and hyperviscosity. The disease has a typical course characterised by a chronic phase lasting several years, and an aggressive terminal phase.

Therapies for myeloma currently consist of the following main classes of agents: proteasome and histone deacetylase inhibitors (bortezomib and panobinostat, respectively), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), corticosteroids, alkylators, anthracyclines, nitrosoureas (to a lesser extent),

plus high-dose chemotherapy and autologous or allogeneic haematopoietic stem cell transplantation (ASCT) for those who are eligible. These agents are combined in clinical practice in an attempt to prolong remission. Specifically, bortezomib has been combined with dexamethasone (VD) + thalidomide (VTD) or lenalidomide (VRD) for induction in young patients, and thalidomide associated with melphalan and dexamethasone (MTD) was used as induction regimen in elderly/frail patients.

Kyprolis (carfilzomib) is an irreversible, tetrapeptide epoxyketone, second-generation proteasome inhibitor. The irreversible binding and higher affinity for the proteasome translates into superior biological activity and cytotoxicity in bortezomib-resistant cell lines *in vitro* and *in vivo*, thus making it suitable for individuals with MM who have progressed following other therapies.

The median progression-free survival for patients using Kyprolis in the pivotal phase 3 trial, used to gain approval for this drug (ASPIRE), was 26.3 months. The median duration of response was 28.6 months and the median duration of treatment was 88 weeks.

Place in Therapy

Kyprolis provides a new option for patients in the terminal phase of MM who have progressed or are resistant to other therapies including bortezomib.

Comparative Pricing

Drug	Estimated Cost per Cycle*	Estimated Annual Cost
Kyprolis™	$9,700 – first 12 cycles $6,500 – cycle 13 and onwards	$123,000 – first year $84,000 – subsequent years
Velcade®	$8,000	$64,000†

*assumes BSA 1.79m^2, no dose sharing; Kyprolis™ cycle=28-days, Velcade® cycle=21 days. † usually given for maximum of 8 cycles.

Impact/Plan Management Suggestions

High impact. Manage similar to Velcade®.

Lenvima™ (lenvatinib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Capsule	02450291 – 10/4mg caps (24mg dose) 02450305 – 10mg caps (20mg dose) 02450313 – 10/4mg caps (14mg dose) 02450321 – 10mg caps (10mg dose)	Eisai Canada	10:00.00 – Antineoplastic agents

Indication(s)

Lenvima (lenvatinib) is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

Dose

The recommended daily dose of lenvatinib is 24mg taken once daily. The daily dose should be reduced as needed according to the dose/toxicity management plan (see Product Monograph). Treatment should continue as long as there is clinical benefit.

Therapeutic Alternatives

Nexavar (sorafenib)

Clinical Notes

Thyroid cancer is rare, representing less than 1% of all cancers. There are three main types of thyroid carcinoma: differentiated, medullary, and anaplastic. Differentiated thyroid cancer (DTC) is the most common of all thyroid cancers accounting for approximately 90% to 95% of cases. The remaining 5% to 10% are either C cell-derived medullary (MTC) or anaplastic (ATC) thyroid carcinomas. The usual treatment of DTC consists of surgery (which can be curative), thyroid-stimulating hormone (TSH)-suppressive thyroid hormone therapy, and use of radioactive iodine (which can also be curative in some cases). For individuals who do not respond to or who are intolerant of these treatments, Lenvima fills a gap in therapy.

Lenvima contains lenvatinib mesilate. Lenvatinib is a receptor tyrosine kinase inhibitor (TKI). The antitumor effects of lenvatinib in patients with thyroid cancer are based primarily on its activity against vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2).

In the pivotal phase 3 trial for Lenvima (SELECT), the overall median progression-free survival was 18.3 months in the lenvatinib group and 3.6 in the placebo group. The median progression-free survival (PFS) was 15.1 months in patients who had previously received treatment with a TKI and 18.7 months in these who were TKI naïve. The median duration of treatment with lenvatinib was 13.8 months.

Place in Therapy

Lenvima provides a treatment option for individuals with radioactive iodine refractory advanced or metastatic differentiated thyroid cancer, including those who have failed prior treatment with sorafenib. There is no comparative data between Lenvima and Nexavar; however, lenvatinib has demonstrated a response rate of 65% compared to 12% for sorafenib with a concomitant longer PFS benefit. The place in therapy will continue to evolve with updated treatment guidelines and further clinical experience.

Comparative Pricing

Drug	Estimated Cost per Month	Estimated Annual Cost
Lenvima™	$7,000	$84,000
Nexavar®	$6,000	$71,000

Impact/Plan Management Suggestions

High impact – Higher cost but potentially more efficacious therapy. Manage with Prior Authorization to ensure appropriate utilization.

Nucala™ (mepolizumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02449781 – 144mg/vial	GlaxoSmithKline Inc.	92:44.00 – Immunosuppressive Agents

Indication(s)

Nucala™ (mepolizumab) is indicated as add-on maintenance treatment of adult patients with severe eosinophilic asthma who:

- are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA), and
- have a blood eosinophil count of ≥ 150 cells/μL (0.15 GI/L) at initiation of treatment with Nucala™ OR ≥ 300 cells/μL (0.3 GI/L) in the past 12 months.

Dose

Nucala™ is given as a fixed dose of 100 mg mepolizumab administered subcutaneously once every 4 weeks.

Therapeutic Alternatives

Xolair (omalizumab)

Clinical Notes

Asthma is a chronic heterogeneous lung disease characterised by inflammation, narrowing of the airways, and reversible airway obstruction. The majority of patients with asthma can be adequately controlled by following step-wise treatment recommendations of both the American Thoracic Society and the Global Initiative for Asthma (GINA). However, a small minority of patients experience uncontrolled asthma despite attempts to control their disease following these recommendations (e.g., high dose inhaled corticosteroids plus additional controller medications). This group of high-risk patients suffers from frequent exacerbations, limited control of symptoms, and compromised quality of life. Exacerbations are particularly disabling for the patient and typically require treatment with high doses of systemic corticosteroids and may require hospital admission. Although patients with uncontrolled severe asthma represent less than 5% of the total asthma population, these patients experience considerable morbidity and are responsible for approximately 50% of total health care costs associated with asthma.

Evidence shows that patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes, including a severe eosinophilic asthma phenotype. Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic airway inflammation despite corticosteroid therapy. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma. Immunoglobulin E (IgE) production and eosinophilic inflammation are promoted by T helper 2 (Th2) cytokines such as IL-5, and to a lesser extent IL-4, and IL-13.

Omalizumab (Xolair®), a recombinant humanised monoclonal antibody (mAb) (IgG1) is recommended for use in GINA Step 5 (add-on treatment for allergic asthma), but only a small proportion of patients with severe asthma are appropriate candidates for its use based on specific weight and IgE levels in addition to a positive test for a perennial allergen. When the omalizumab label criteria are applied to the severe eosinophilic asthma population, there is approximately a 30% overlap with the mepolizumab target population.

Mepolizumab is a recombinant humanised IgG (IgG1 kappa) mAb which binds with high specificity and affinity to human interleukin 5 (IL-5), preventing it from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting IL-5 signalling. IL-5 has been identified as the key cytokine responsible for regulation of blood and tissue eosinophils (the growth and differentiation, recruitment, activation and survival of eosinophils).

The overproduction of IL-5 in the airways has been specifically reported in patients with eosinophil-associated asthma. By targeting IL-5, mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signalling and the overexpression of peripheral blood and tissue eosinophils. However, complete blood eosinopenia is not possible due to redundant signalling by IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF) through a common β-sub-unit. In addition, available data do not indicate that reduction of eosinophils has any untoward effects on normal health; patients lacking eosinophils in association with immunodeficiency or as a consequence of IgG-mediated eosinophil precursor destruction do not display any distinguishing abnormalities related to the eosinophil reduction.

Place in Therapy

Nucala is indicated for and should be used in the specific phenotype of patients with severe uncontrolled asthma despite high-dose ICS combined with other controller therapies who have concurrently high blood eosinophil levels. The other drug for severe asthma, Xolair (omalizumab), which only partially overlaps with this patient population is effective in only a small proportion of patients eligible for omalizumab therapy (estimated 30-50% efficacy rate).

Comparative Pricing

Drug	Estimated Annual Cost
Nucala™	$26,000
Xolair®	$8,500 - $51,000

Impact/Plan Management Suggestions

High impact – minimal cost shift from comparable therapy (Xolair®). Manage with Prior Authorization to ensure appropriate utilization.

Orkambi™ (ivacaftor/lumacaftor)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02451379 – 125mg/ 200mg	Vertex Pharmaceuticals (Canada) Inc.	48:14.12 – Cystic Fibrosis Transmembrane Conductance Regulator Potentiators

Indication(s)

Orkambi (lumacaftor/ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Dose

The recommended dose is two tablets (each containing lumacaftor 200 mg / ivacaftor 125 mg) taken orally every 12 hours (lumacaftor 800 mg / ivacaftor 500 mg total daily dose) with fat-containing food.

Therapeutic Alternatives

None

Clinical Notes

Cystic fibrosis (CF) is a chronically debilitating, autosomal recessive disease associated with serious morbidity and a high rate of premature mortality and at present, there is no cure. CF affects approximately 70,000 individuals worldwide, including approximately 4,000 individuals in Canada.

CF is caused by mutations in the CF transmembrane conductance regulatory (CFTR) gene that result in absence or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride ion (CL-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, that is responsible for aiding in the regulation of salt and water absorption and secretion. The most prevalent CFTR mutation is an in-frame deletion in the CFTR gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR): it prevents most of the CFTR protein from reaching the cell surface, resulting in little-to-no chloride transport. Patients who are homozygous with F508del-CFTR defects have little or no CFTR protein at the cell surface and hence suffer from a severe form of CF disease. The failure of the mutated CFTR to function properly in the lungs result in a cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs and eventually respiratory failure, the most common cause of death for patients with CF. The predicted median age of survival of individuals born with CF today is approximately 40 years of age, while the median age at death is generally in the 20s.

Lumacaftor has been clinically developed in combination with ivacaftor as a fixed dose combination (FDC) tablet for oral administration for the treatment of CF. Lumacaftor is a new active substance, while ivacaftor is a known active substance that is authorised as Kalydeco® for the treatment of CF in patients aged 6 years and older who have one of the following gating mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

Lumacaftor (LUM; VX-809) is a CFTR corrector and ivacaftor (IVA; VX-770; Kalydeco®) is a CFTR potentiator. LUM acts on CFTR to facilitate the cellular processing and trafficking of CFTR, allowing the protein to reach the cell surface, where it exhibits improved chloride channel function compared to uncorrected F508del-CFTR. The channel gating activity of F508del-CFTR that has been delivered to the cell surface by LUM can be potentiated by IVA to further enhance chloride transport. The combination of a CFTR corrector and potentiator is a novel approach to enhance the amount and function of the defective CFTR protein in patients with CF who have the F508del-CFTR mutation.

Of approximately 4,000 CF patients in Canada, it is estimated that half of these would be homozygous for F508del-CFTR. Also, approximately 72.2% of these would be ≥ 12 years of age which means that approximately 1,500 Canadians would be eligible for Orkambi treatment.

Place in Therapy

Orkambi is the first and only available CF disease modifying drug for patients homozygous for *F508del* mutation. This mutation is present in about half of all CF patients.

Comparative Pricing

Drug	Estimated annual cost
Orkambi™	$260,000
Kalydeco®*	$320,000

*for cost comparison purposes only, Kalydeco is not indicated for the same patient population as Orkambi

Impact/Plan Management Suggestions

High impact. Manage with Prior Authorization to ensure appropriate utilization.

Uptravi® (selexipag)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02451158 – 200mcg 02451166 – 400mcg 02451174 – 600mcg 02451182 – 800mcg 02451190 – 1,000mcg 02451204 – 1,200mcg 02451212 – 1,400mcg 02451220 – 1,600mcg	Actelion Pharmaceuticals Ltd.	48:48.00 – Vasodilating Agents

Indication(s)

Uptravi® is indicated for the long-term treatment of idiopathic pulmonary arterial hypertension (iPAH), heritable pulmonary arterial hypertension (HPAH), PAH associated with connective tissue disorders and PAH associated with congenital heart disease, in adult patients with WHO functional class (FC) II–III to delay disease progression. Disease progression included: hospitalization for PAH, initiation of intravenous or subcutaneous prostanoids, or other disease progression events (decrease of 6-minute walk distance [6MWD] associated with either worsened PAH symptoms or need for additional PAH-specific treatment).

Dose

The goal is to reach the individually appropriate dose for each patient (the individualised maintenance dose). The recommended starting dose of Uptravi is 200 micrograms given twice daily, approximately 12 hours apart. The dose is increased in increments of 200 micrograms given twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1600 micrograms twice daily is reached. During dose titration, it is recommended not to discontinue treatment in the event of expected pharmacological side effects, since they are usually transient or manageable with symptomatic treatment. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level.

Therapeutic Alternatives

Oral agents

Endothelin Receptor Antagonists (ERAs): Tracleer (bosentan)*; Volibris (ambrisentan); Opsumit (macitentan)

Phophodiesterase-5 (PDE-5) Inhibitors: Revatio (sildenafil)*; Adcirca (tadalafil)

Soluble Guanylate Cyclase Stimulator: Adempas (riociguat)

Intravenous injections

Prostacyclin Analogues: Flolan, Caripul (epoprostenol sodium); Remodulin (treprostinil sodium)

*generics available

Clinical Notes

The vascular protective effects of prostacyclin (PGI2) are mediated by the prostacyclin receptor (IP receptor). Decreased expression of IP receptors and decreased synthesis of prostacyclin contribute to the pathophysiology of PAH.

Selexipag is an oral, selective, IP receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogues.

Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. Selexipag improves haemodynamic variables and prevents cardiac and pulmonary remodelling in a rat model of PAH. In these PAH rats, pulmonary and peripheral vasodilation in response to selexipag correlate, indicating that peripheral vasodilation reflects pulmonary pharmacodynamic efficacy. Selexipag does cause neither IP receptor desensitisation *in vitro* nor loss of response in a rat model.

PAH patients have variable degrees of IP receptor expression. Differences in the maintenance dose of selexipag between individuals may be related to differences in IP receptor expression levels.

Place in Therapy

Uptravi can be used as an alternative to injectable prostacyclin analogues. It can also be used in combination with other classes of drugs used to treat PAH such a PDE-5 inhibitors and ERAs. Although only marginal improvements in exercise capacity were shown, it has been shown to delay disease progression.

Comparative Pricing

Drug	Estimated annual cost
Uptravi®	$49,000 (after initial dose titration)
bosentan	$24,000
sildenafil	$8,000
Adempas®	$49,000

Impact/Plan Management Suggestions

High impact – low utilization but high cost. The titration phase of treatment will need to be managed to prevent excessive costs resulting from multiple tablet use.

Zepatier™ (elbasvir/grazoprevir)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02451131 – 50/100mg	Merck Canada Inc.	08:18.40 – HCV Antivirals

Indication(s)

Zepatier™ (elbasvir/grazoprevir) is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infections in adults as follows:

Without ribavirin (RBV):

- in genotype (GT) 1 or 4 treatment-naïve (TN) and peginterferon alfa + ribavirin (PR) treatment-experienced (TE) relapsers (12 weeks)
- in GT1 protease inhibitor (PI)/PR-TE relapsers (12 weeks)
- in GT1b TN, non-cirrhotic patients (8 weeks)
- in GT1b PR- or PI/PR-TE on-treatment virologic failures (12 weeks)

With ribavirin (RBV):

- in GT1a PR- or PI/PR-TE on-treatment virologic failures (16 weeks)
- in GT4 PR-TE on-treatment virologic failures (16 weeks)

With sofosbuvir (SOF):

- in GT3 TN patients (12 weeks)

Dose

The recommended dosage of Zepatier™ is one tablet taken orally once daily with or without food. Duration of treatment dependent upon indication (see above and see product monograph for further details.)

Clinical Notes

Zepatier is a fixed-dose combination of two direct-acting antiviral agents with distinct mechanisms of action and nonoverlapping resistance profiles to target the hepatitis C virus (HCV) at multiple steps in the viral lifecycle. Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

Place in Therapy

Zepatier is the first treatment to be recommended for individuals who have failed with protease inhibitor treatment combined with peginterferon/ribavirin. Zepatier has been incorporated into the latest revision of the AASLD/IDSA Hepatitis C Virus Guidance. It is essentially in line with the table below under Therapeutic Alternatives except resistance testing is recommended for certain patients with GT1a disease, and use in GT3 disease is not recommended. These updated guidelines also recommend Zepatier for use in patients with Stages 4 or 5 chronic kidney disease (creatinine clearance < 30ml/min or end-stage renal disease) for patients with GT 1a, 1b, or 4 infection.

Therapeutic Alternatives and Comparative Pricing

Zepatier unit cost: $717.86

There are no dose adjustments required for the presence or absence of cirrhosis.

Patient Population	Regimen	Duration (weeks)	Cost
GT1a TN	**Zepatier**	**12**	**$60,300**
	Harvoni	12 (8)[a]	$71,000 ($47,000)
	Holkira Pak + RBV[b]	12	$59,000
	Sovaldi + Galexos[c]	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1b TN	**Zepatier**	**12 (8)***	**$60,300 ($40,200)***
	Harvoni	12 (8)[a]	$71,000 ($47,000)
	Holkira Pak	12	$59,000
	Sovaldi + Galexos	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1a PR- or PI/PR-TE Relapsers	**Zepatier**	**12**	**$60,300**
	Harvoni +/- RBV[f]	12-24[e]	$74,000 - $141,000
	Holkira Pak + RBV[b]	12	$59,000
	Sovaldi + Galexos	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1b PR-- orPI/PR-TE Relapsers	**Zepatier**	**12**	**$60,300**
	Harvoni +/- RBV[f]	12-24[e]	$74,000 - $141,000
	Holkira Pak + RBV[b]	12	$59,000 - $118,000
	Sovaldi + Galexos	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1a PR- or PI/PR-TE on-treatment virologic failures	**Zepatier + RBV**	**16**	**$84,684 - $85,541**
	Harvoni +/- RBV[f]	12-24[e]	$74,000 - $141,000
	Holkira Pak + RBV	24	$118,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1b PR- or PI/PR-TE on-treatment virologic failures	**Zepatier**	**12**	**$60,300**
	Harvoni +/- RBV[f]	12-24[e]	$74,000 - $141,000
	Holkira Pak +/- RBV[b]	12	$59,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]

(continued next page)

Patient Population	Regimen	Duration (weeks)	Cost
GT3 TN	**Zepatier + Sovaldi**	**12**	**$118,325**
	Sovaldi + RBV[f]	24	$123,000 - $124,000
	Harvoni + RBV (off-label)[f]	12	$74,000 - $75,000
	Daklinza + Sovaldi[h]	12	$96,000 - $134,000g
GT4 TN or PR-TE Relapsers	**Zepatier**	**12**	**$60,300**
	Technivie + RBV[b]	12	$59,000
	Harvoni (off-label)	12	$71,000
	Sovaldi + RBV[f]	24	$123,000 - $124,000
GT1b PR- or PI/PR-TE on-treatment virologic failures	**Zepatier + RBV**	**16**	**$84,684 - $85,541**
	Technivie + RBV[b]	12	$59,000
	Harvoni (off-label)	12	$71,000
	Sovaldi + RBV[f]	24	$123,000 - $124,000

Abbreviations: see under Indications. Only interferon-free treatments considered. From CASL chronic hepatitis C guidelines; second-line treatments are highlighted in grey.

* an 8-week treatment course may be considered for GT1b TN without cirrhosis or significant fibrosis (e.g., METAVIR F0-F2)

a an 8-week treatment course may be used for individuals with no cirrhosis and pre-treatment HCV RNA < 6 million U/ml

b RBV with Holkira Pak/Technivie is Moderiba which is available at no additional cost from AbbVie.

c second-line treatments are highlighted in grey

d treatment duration dependent upon presence or absence of cirrhosis (12-weeks for absence; 24-weeks for presence)

e 12-week treatment duration for Harvoni combined with RBV, 24-week treatment duration for Harvoni alone

f RBV- weight based dosing: 1000mg/day, < 75kg; 1200mg/day, ≥ 75kg; administered twice daily.

g usual Daklinza dose is 60mg once daily but may be modified to 30mg or 90mg once daily in case of potential drug-drug interactions with strong inhibitors or moderate inducers of CYP3A4 (e.g., with concomitant HIV therapy).

h DCV-SOF treatment only cost-effective and recommended for patients without cirrhosis

Impact/Plan Management Suggestions

High Impact – while potentially more cost effective than available therapies continues to be high cost.

FIRST TIME GENERICS

First Time Generic Drugs (Notices of Compliance (NOCs) from November 28, 2015 to February 24, 2016)

Generic Name	Reference Drug (Brand)	Rank by ingredient cost in 2015	Manufacturer	Route of Administration	Approved Indications/ Comments
pemetrexed disodium	Alimta	1131	Hospira Healthcare Corp.	intravenous	malignant pleura mesothelioma, nonsquamous non-small cell lung cancer
nitric oxide	Inomax	—	Air Liquide Healthcare America Corp.; Praxair Canada Inc.	inhalation	neonatal hypoxic respiratory failure

Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the January to March 2016 DEC Meetings

NEW DRUGS AND PRODUCT LINE EXTENSIONS

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from November 28, 2015 to February 24, 2016)

Band name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Invega Sustenna	paliperidone palmitate	Janssen Inc.	Intramuscular injection	New indication	For maintenance treatment of schizoaffective disorder
Fycompa	perampanel	Eisai Ltd.	Tablet	New indication	Expansion to include management of primary generalized tonic-clonic (PGTC) seizures in adult patients with epilepsy.
Beteflam	betamethasone valerate	Cipher Pharmaceuticals Inc.	Topical patch	New dosage form	Patch is efficacy similar to topical cream/ointment under an occlusive dressing. Only indicated for mild-moderate plaque psoriasis of elbows and knees in adults.
Forxiga	dapagliflozin	AstraZeneca Canada Inc.	Tablet	New indication	Extension to include use as add-on therapy to metformin in combination with a sulfonylurea which brings Forxiga in line with other SGLT2 inhibitors.
Xigduo	dapagliflozin/ metformin	AstraZeneca Canada Inc.	Tablet	New drug combination	Fixed-dose combination product combining Forxiga with metformin in a twice daily administered tablet.
Eylea	aflibercept	Bayer Inc.	Intravitreal injection	New indication	Expansion of indication to include use to treat visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO).
Stelara	usetkinumab	Janssen Inc.	Subcutaneous injection	New indication	Extension of treatment population for plaque psoriasis to 12 to 17 year-olds from adults only.
Humira	adalimumab	AbbVie Corp.	Subcutaneous injection	New indication	Hidradenitis Suppurativa
Afinitor	everolimus	Novartis Pharmaceuticals Canada Inc.	Tablet	New strength	7.5mg
Bridion	sugammadex sodium	Merck Canada Inc.	Intravenous injection	New drug	New drug for use in hospital for post-surgical reversal of neuromuscular blockade.
Viacoram	perindopril arginine/ amlodipine	Servier Canada	Tablet	New drug combination	Fixed-dose combination of the ACE inhibitor perindopril with the calcium channel blocker amlodipine for use in mild to moderate hypertension.

(continued next page)

NEW DRUGS AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from November 28, 2015 to February 24, 2016)

Band name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Kovaltry	octocog alfa, recombinant antihemophilic factor	Bayer Inc.	Intravenous injection	New brand	Recombinant coagulation Factor VIII for use in prevention or treatment of bleeding episodes in patients with hemophilia A.
Jadenu	deferasirox	Novartis Pharmaceuticals Canada Inc.	Tablet	New brand/ New formulation	Film coated tablet form of deferasirox which is an alternative to the dissolvable tablet form of the drug, Exjade.
Jetrea	ocriplasmin	Alcon Canada Inc.	Intravitreal injection	New strength	New strength which eliminates need for dilution. Dose can be injected directly. For use in treatment of symptomatic vitreomacular adhesion.
Visanne	dienogest	Bayer Inc.	Tablet	New indication	Extension of indication to include patients under the age of 18 after menarche.
Ciloxan	ciprofloxacin hydrochloride	Alcon Canada Inc.	Ophthalmic solution	New indication	Indication revised to remove otic indication and administration.
Volibris	ambrisentan	GlaxoSmithKline Inc.	Tablet	New indication	New indication to allow for combination therapy of this endothelin receptor antagonist with the phosphodiesterase-5 inhibitor, tadalafil for pulmonary arterial hypertension.

Authors: Aaron Aoki, RPh, BScPhm, MBA, CDE, CRE; Moe Abdallah, B.Sc., B.Sc.Phm; Paul Thompson, B.Sc.Phm, RPh; Camille Gagnon, PharmD; Priscilla Po, PharmD, RPh