Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the January to March 2017 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

Kevzara™ (sarilumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02460521 – 150mg/1.14ml PFS 02460548 – 200mg/1.14ml PFS	Sanofi-Aventis Canada Inc.	92:36.00 – Disease-Modifying Antirheumatic Agents

Indication(s)

Kevzara (sarilumab) is indicated in the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more biologic or non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Dose

The recommended dose of Kevzara is 200 mg once every 2 weeks given as a subcutaneous injection. Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and elevated liver enzymes.

Therapeutic Alternatives

Actemra (tocilizumab) [IV and SC; N.B. SC formulation only indicated for RA]

Clinical Notes

Kevzara (sarilumab) is a fully human monoclonal antibody (mAb) directed against the interleukin-6 (IL-6) receptor α (IL-6Rα) that binds membrane-bound and soluble human IL-6Rα with high affinity thereby blocking cis and trans IL-6-mediated inflammatory signalling cascade, and with no evidence of complement-dependent or antibody-dependent cell-mediated cytotoxicity. IL-6 is a key driver of inflammation, and is elevated in the serum and synovial fluid of patients with RA. Kevzara has a similar mechanism of action to tocilizumab (Actemra).

The approval of Kevzara was based on the evidence from two randomized, double-blind, placebo controlled multicenter studies, MOBILITY and TARGET, in patients 18-years and older with moderately to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria.

MOBILITY (N=1369) consisted of two parts: Part A was a dose ranging Phase 2 trial which then rolled into an expanded Phase 3 trial which was Part B. The objective of MOBILITY Part B was to evaluate the efficacy and safety of Kevzara plus methotrexate (MTX) versus placebo in combination with MTX. Kevzara + MTX significantly improved RA disease scores compared to placebo + MTX at 24 weeks, which was maintained to 52 weeks. Kevzara also significantly reduced structural joint damage at 52 weeks compared with MTX alone.

The objective of the TARGET trial (N=546) was to assess the efficacy and safety of sarilumab, administered with concomitant conventional DMARDs, in patients with moderately to severely active RA with a history of inadequate response to or intolerance of TNF antagonists. Statistically significant improvements were seen with sarimumab in primary endpoints at 24 weeks.

Supporting data in an unpublished trial (ASCERTAIN) assessing the safety of sarilumab compared to tocilizumab showed no clinically meaningful differences between the two anti- IL-6Rα agents.

Place in Therapy

Kevzara is a biologic DMARD which provides an alternate mechanism of action to TNF-α inhibitors. While the mechanism of action is comparable to Actemra (tocilizumab), the dose of Kevzara and hence its cost is more predictable.

Comparative Pricing

Drug	Estimated Annual Cost
Kevzara	$18,000
Actemra SC	$9,750 - $19,500
Actemra IV	$6,100 - $27,300

Impact

Intermediate impact – high cost treatment but potential cost shift from higher cost treatments.

Lancora™ (ivabradine)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02459973 – 5mg 02459981 – 7.5mg	Servier Canada Inc.	24:04.92 – Miscellaneous Cardiac Drugs

Indication(s)

Lancora (ivabradine) is indicated for the treatment of stable chronic heart failure with reduced left ventricular ejection fraction (≤ 35%) in adult patients with NYHA Classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 beats per minute, to reduce the incidence of cardiovascular mortality and hospitalisations for worsening heart failure. Lancora should be administered in combination with standard chronic heart failure therapies.

Dose

Lancora 5 mg twice daily is the recommended starting dose for patients with stable chronic heart failure who are in sinus rhythm with a resting heart rate at or above 77 beats per minute.

After two weeks of treatment, assess the patient and adjust the dose based on the patient's resting heart rate according to the instructions provided in the product monograph. The maximum dose of Lancora is 7.5 mg twice daily.

Therapeutic Alternatives

Entresto (sacubatril/valsartan)

Clinical Notes

The active ingredient in Lancora is ivabradine. Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.

The main pharmacodynamic property of ivabradine in humans is a specific dose-dependent reduction in heart rate. At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and heart muscle oxygen consumption. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

- in clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
- in patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any negative effects on LVEF.

The symptoms of heart failure are caused by the heart not pumping enough blood around the body. By lowering the heart rate, ivabradine reduces the stress on the heart, thereby slowing the progression of heart failure and improving symptoms.

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6,505 adult patients with stable chronic heart failure (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF ≤ 35%) and a resting heart rate ≥ 70 bpm. This was the pivotal study leading to the approval of Lancora for heart failure.

Patients received standard care including beta-blockers (89%), ACE inhibitors or angiotensin II antagonists (ARB) (91%), diuretics (83%), and mineralocorticoid receptor antagonist (60%). In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure. The most significant safety issue is excessively low heart rate which is due to the pharmacologic effect of the drug.

Place in Therapy

Three major heart failure guideline organizations (Canadian Cardiovascular Society [CCS], European Society of Cardiology [ESC], American College of Cardiology/American Heart Association/Heart Failure Society of America [ACC/AHA/HFSA]) are in overall agreement: ivabradine may be considered after standard evidence-based triple therapy for heart failure has been attempted (i.e., beta-blocker [either patient refractory or intolerant] + ACE inhibitor/ARB + mineralocorticoid receptor antagonist) and patient remains symptomatic, provided the patient meets the LVEF (≤ 35%) and HR (≥ 77 bpm) criteria noted above. Lancora may be used in a similar population of patients as Entresto.

Comparative Pricing

Drug	Estimated Annual Cost
Lancora	$650 - $1,200
Entresto	$2,750

Impact

Minimal impact – relatively small patient population with moderate level of spend.

Mictoryl®/Mictoryl® Pediatric (propiverine HCl)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Capsule / Tablet	02460262 – 30mg 02460270 – 45mg 02460289 – 5mg	Duchesnay Inc.	12:08.08 Parasympatholytic (Cholinergic Blocking) Agents Antimuscarinic Antispasmodics

Indication(s)

Mictoryl/Mictoryl Pediatric (propiverine hydrochloride) is indicated for symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder (OAB).

Dose

Adults:

For the treatment of OAB, the recommended dose is one capsule containing 30mg propiverine hydrochloride once daily. If the dose is well tolerated and clinical effect is not improved adequately, the dose may be increased to 45 mg. The maximum recommended daily dose is 45 mg.

Pediatrics:

For the treatment of OAB in the pediatric population, a standard daily average of 0.8 mg/kg body weight administered in two doses is recommended. For children weighing less than 35 kg, a body weight adjusted dosing is achievable with Mictoryl Pediatric 5mg tablets for OAB. In children or adolescents with a body weight over 35 kg, the maximum recommended dose is 30 mg administered in two daily doses.

Therapeutic Alternatives

Ditropan, Ditropan XL (oxybutynin HCl)*; Vesicare (solifenacin succinate)*; Detrol, Detrol LA (tolterodine tartrate)*; Enablex (darifenacin HBr)*; Toviaz (fesoterodine fumarate); Trosec (trospium Cl); Myrbetriq (mirgabetron)

*Generics available

Clinical Notes

Studies show that OAB symptoms (frequent urination, urgency, incontinence) negatively influence health-related quality of life and increase anxiety and depression. It is estimated that OAB affects 18.1% of Canadians (14.8% of men and 21.2% of women), and increases with age. For patients who fail behavioral therapies (e.g., bladder training), pharmacotherapy is often considered.

Mictoryl is an antimuscarinic agent with a mixed mode of action in the treatment of symptoms associated with OAB. As well as blocking muscarinic receptors in the detrusor muscle, the drug also inhibits cellular calcium influx, thereby diminishing muscle spasm.

The efficacy of Mictoryl was evaluated in two randomized, placebo and/or active controlled parallel group, multicenter, clinical trials in adult patients with overactive bladder having symptoms of urinary frequency, urgency and/or urge urinary incontinence. These studies demonstrated statistically significant decreases in incontinence episodes and voiding episodes per 24 hours compared to placebo and active treatment. Adverse drug reactions were of comparable frequency with other anticholinergic therapies.

A randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial was also performed in the pediatric population (age 5-10). The primary endpoint showed a decrease in voiding daily frequency vs placebo. Mictoryl was generally well tolerated in children.

Place in Therapy

Mictoryl represents a new option of treatment for adult and pediatric patients suffering from OAB. Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile and ease of use, as well as cost.

Pricing

Drug	Estimated Annual Cost
Mictoryl	$405-510
generic oxybutynin 5mg tab	$75
Ditropan XL 10mg tab	$900
generic tolterodine LA 4mg cap	$180
generic solifenacin 10mg tab	$155
Enablex 7.5mg SR Tab	$620
Toviaz 8mg tab	$580
Myrbetriq 25mg	$565
Gelnique 100mg/g gel	$765

Impact

Minimal impact – cost-shift from other treatment options.

Rapivab™ (peramivir)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02460319 – 10mg/mL	BioCryst Pharmaceuticals Inc.	08:18.28 – Neuraminidase Inhibitors

Indication(s)

Rapivab is indicated for the treatment of acute uncomplicated influenza in patients 18 years and older, who have been symptomatic for no more than 2 days.

Dose

The recommended dose of Rapivab in adult patients 18 years of age or older with acute uncomplicated influenza is a single 600 mg dose (3 vials), administered via intravenous infusion, for 15 to 30 minutes.

Administer Rapivab within 2 days of onset of symptoms of influenza.

Therapeutic Alternatives

Tamiflu (oseltamivir)*; Relenza (zanamivir)

*Generic available

Clinical Notes

Seasonal influenza is an acute respiratory illness caused by influenza A or B viruses. Influenza occurs in outbreaks and epidemics worldwide, mainly during the winter season. In some high-risk populations, it is associated with increased morbidity and mortality.

Neuraminidase inhibitors are active against influenza A and B strains. Peramivir joins 2 antivirals who are already part of this category in Canada: zanamivir and oseltamivir. Early treatment (within 24 to 30 hours of onset of fever and other symptoms) with these therapies can shorten the duration of influenza symptoms by approximately one-half day to three days. Some studies show that antiviral therapy reduces severity, incidence and complications of influenza, as well as length of hospital stay and mortality in those hospitalized. However, some studies in immunocompetent patients have not shown a reduction in complications.

Peramivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells. Peramivir has a strong and prolonged affinity for influenza virus neuraminidase, thus can be administered as a single intravenous dose. The efficacy of peramivir was evaluated in a trial of 297 patients with influenza infection. Individuals who received peramivir 600 mg had their influenza symptoms alleviated an average of 21 hours sooner and became afebrile approximately 12 hours sooner than those who received placebo. Another study compared peramivir to oseltamivir, and evaluated peramivir to be non-inferior to oseltamivir. Diarrhea is the most common adverse effect reported with peramivir. Some serious adverse effects include hypersensitivity reactions such as Stevens-Johnson syndrome or erythema multiforme.

Place in Therapy

Rapivab is a new option of treatment of influenza virus for patients who may not be able to take oral or inhaled treatment. Additionally, one-dose IV administration will facilitate adherence.

Pricing

Drug	Estimated Treatment Cost
Rapivab	Pricing not available
Tamiflu 75mg cap	$45 every 5 days
generic oseltamivir 75mg cap	$32 every 5 days
Relenza 5mg PDR INH	155 every 5 days

Impact

Minimal impact – drug is expected to be administered and funded in the hospital setting.

Rexulti™ (brexpiprazole)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02461749 – 0.25 mg 02461757 – 0.5 mg 02461765 – 1 mg 02461773 – 2 mg 02461781 – 3 mg 02461803 – 4 mg	Otsuka Canada Pharmaceutical Inc.	28:16.08 Atypical Antipsychotics

Indication(s)

Rexulti is indicated for treatment of schizophrenia in adults.

Dose

The recommended starting dosage for Rexulti is 1 mg once daily on Days 1 to 4, taken orally with or without food.

The recommended target Rexulti dosage is 2 mg to 4 mg once daily. In clinical trials, the dose was titrated to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

Therapeutic Alternatives

Abilify (aripriprazole); Clozaril (clozapine)*; Invega (paliperidone); Latuda (lurasidone); Risperdal (risperidone)*; Saphris (asenapine); Seroquel/Seroquel XR (quetiapine)*; Zeldox (ziprasidone); Zyprexa/Zyprexa Zydis (olanzapine)*

*Generics available

Clinical Notes

Schizophrenia is a chronic, progressive and disabling mental illness with a broad range of symptoms that lead to loss of function and poor quality of life. Schizophrenia affects approximately 1% of the population (roughly 350,000 Canadians). Average onset of disease is 18 years for men, and 25 years for women – both sexes being affected in equal numbers. Life expectancy of schizophrenia patients is reduced by 15 to 20 years, leading causes of death include cardiovascular disease and suicide. Caregiver burden in schizophrenia is significant and can lead to several work, financial and social difficulties in family members.

Rexulti is a novel oral second generation antipsychotic (SGA). Rexulti's efficacy is thought to be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors as well as antagonist activity at serotonin 5-HT2A receptors. This mechanism of action is similar to aripiprazole (Abilify) and differs from the other atypical antipsychotics which function as receptor antagonists. Additionally, Rexulti acts as a partial agonist at dopamine D3 receptors and as an antagonist at serotonin 5HT2B and 5HT7 and noradrenergic α1A, α1B, α1D, and α2C receptors. Rexulti also exhibits affinity for the histamine H1 receptor and for the muscarinic M1 receptor.

The efficacy of Rexulti was established in two Phase III, 6-week, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with schizophrenia (VECTOR and BEACON). Rexulti was also evaluated in EQUATOR, a multicenter, randomized, double-blind, placebo-controlled Phase III 52-week study.

In VECTOR (n=623), at Week 6, Rexulti 2 mg and 4 mg once daily were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In BEACON (n=657), at Week 6, Rexulti 4 mg once daily was superior to placebo on the PANSS total score. Rexulti 1 mg and 2 mg once daily treatment arms showed numerical improvements in PANSS total score compared with placebo but were not statistically superior.

In EQUATOR, patients who were initially stabilized on Rexulti (n=202) were randomly assigned to receive placebo or Rexulti 1-4mg once daily. EQUATOR measured the time to exacerbation of psychotic symptoms/impending relapse. Rexulti 1-4mg (mean average daily dose: 3.6mg) demonstrated a statistically significantly delayed time to relapse compared to placebo.

In a pooled analysis of cumulative safety and tolerability data from BEACON and VECTOR studies, most frequent reported treatment-emergent adverse events (incidence of ≥2% and greater than placebo) were diarrhea, dyspepsia, weight increases (average +1.2kg), akathisia, sedation and tremor. EPS-related adverse events (ex: akathisia, parkinsonian events, etc) were reported in 14% of Rexulti 4mg patients, 9.8% of Rexulti 2mg patients and 8.4% of placebo patients. The long-term study EQUATOR showed a treatment-emergent adverse events discontinuation rate of 8.8% during its stabilization phase, during which 9.1% of patients showed akathisia, 11.3% potentially clinically relevant weight increase (≥7% increase - mean weight increase of 0.8kg) and 12.1% insomnia rates. Maintenance phase did show lower rates of adverse events, as would be expected since only responding patients were included.

Place in Therapy

Canadian treatment guidelines for schizophrenia date back to 2005 and are expected to be updated in 2017. In 2005, the guideline already indicated SGAs to be increasingly replacing first-generation antipsychotics (FGAs) as first-line treatment, and underlined differing side effect profiles between both – SGAs inducing fewer neurologic side effects but with greater propensity for metabolic side effects.

Rexulti appears to be an effective agent for the treatment of schizophrenia based on limited, placebo-controlled data only. Rexulti has a similar proposed mechanism of action to that of aripiprazole, making these two atypical antipsychotics the only agents with partial agonist activity at the dopamine D2 and serotonin 5HT1A receptors; the other atypical antipsychotics function as antagonists. Based on non-direct comparison, common AEs for Rexulti appear similar to aripiprazole. Rexulti represents a new option of treatment in an already crowded drug class with several existing oral or injectable comparators.

Pricing

Drug	Estimated Annual Cost
Rexulti	$1,300
Abilify	$1,700 - $2,000
Invega	$2,200
Latuda	$1,600
Zeldox	$1,600
generic quetiapine XR	$400
generic risperidone	$450

Impact

Minimal impact – expect cost-shift from similarly priced alternatives.

Viberzi™ (eluxadoline)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02460890 – 75mg 02460904 – 100mg	Allergan Pharma Co.	56:92.00 – Miscellaneous GI Drugs

Indication(s)

Viberzi (eluxadoline) is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

Dose

The recommended dosage of Viberzi is 100 mg taken orally twice daily with food.

For patients who are unable to tolerate the 100 mg dose, the recommended dosage of Viberzi is 75 mg taken orally twice daily with food.

For patients 65 years or older, the starting dose should be 75 mg twice daily with food. If the 75 mg BID dose is well tolerated but not efficacious, the dose could be increased to 100 mg twice daily.

Therapeutic Alternatives

No alternatives approved for this indication in Canada. Off-label use of Zaxine (rifaxamin, approved for this use in US).

Clinical Notes

Viberzi (eluxadoline) is a peripherally acting mixed μ-opioid receptor agonist–δ-opioid receptor antagonist and κ-opioid receptor agonist with minimal oral bioavailability. Viberzi acts locally within the gastrointestinal (GI) tract, where the extensive expression of opioid receptors is believed to play a key role in regulating GI motility, secretion, and visceral sensation.

Irritable bowel syndrome (IBS) is a functional bowel disorder affecting up to 20% of adolescents and adults in North America, with a higher prevalence in women. The diagnosis of IBS is based on the symptom-based Rome III criteria and is defined as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool. Some estimates state that as many as five-million Canadians suffer from IBS with 120,000 developing it each year. Diarrhea predominant IBS (IBS-D) accounts for approximately one-third of all cases of IBS and is defined as IBS with loose or watery stools with ≥25% of bowel movements.

Currently, there are no pharmacologic treatments available in Canada for IBS-D. Treatments that have been used include anti-diarrheal medications such as loperamide. While effective for reducing the frequency of loose bowel movements, it has no effect on the other symptoms of IBS, particularly abdominal pain with is associated with all forms of IBS (diarrhea predominant, constipation predominant, and mixed types). Bile acid sequestrants such as cholestyramine, colestipol, and colesevelam have also been used with limited success for this condition. Similar to loperamide, while reducing bowel frequency and improving stool consistency, their effect on abdominal pain relief and bloating is limited. In the US, rifamaxin (Zaxine in Canada) has been approved for use in IBS-D. This would be considered as off-label use in Canada.

Viberzi was approved based on two pivotal randomized, multi-center double-blind, placebo-controlled trials with identical designs for the first 26-weeks. IBS-3001 (N=1,280) provided double-blind treatment for a total of 52 weeks, while IBS-3002 (N=1,145) ended treatment at 26 weeks. Efficacy data collection ended for both trials after 26 weeks. The primary efficacy end-point for both trials was a composite response of abdominal pain reduction and improvement of stool consistency.

Secondary end-points included these individual components as well a global symptom score, patient evaluated relief of IBS symptoms and change in IBS-QOL questionnaire score. Significant improvements in the primary efficacy end-point were seen at 12-weeks in both trials and in the pooled results for both 75mg and 100mg doses, while at 26 weeks this was only seen consistently for the 100mg dose in each individual trial, while the pooled data at 26 weeks showed significant improvements with both doses. There was no significant overall reduction in abdominal pain demonstrated except when more stringent measures of pain reduction were applied such as reductions in pain of 30, 40 or 50% or more.

Place in Therapy

Viberzi is a modestly effective treatment to improve stool consistency in patients with IBS-D. Improvement in abdominal pain was not statistically significant vs. placebo when evaluated separately from the overall composite responder rate (except as noted previously). Viberzi has been studied in men and women and was found to be similarly effective regardless of gender. Treatment options for IBS-D are limited, with Viberzi currently being the only drug approved in Canada for the treatment of IBS-D.

Pricing

Drug	Estimated Annual Cost
Viberzi	Pricing not available
generic loperamide 2mg	$110
Zaxine 550mg [off-label]	$350- $1,021

Impact

Insufficient information.

Zinbryta™ (daclizumab beta)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02459620 – 150mg/ml (pre-filled syringe) 02459639 – 150mg/ml (pre-filled pen)	Biogen Canada Inc.	92:20.00 – Immunomodulatory Agents

Indication(s)

Zinbryta (daclizumab beta) is indicated for the treatment of adult patients with active relapsing remitting multiple sclerosis (RRMS) who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis (MS). The safety and efficacy of Zinbryta have not been established in patients with primary and secondary progressive MS.

Dose

The recommended dose of Zinbryta is 150 mg injected subcutaneously once a month.

Therapeutic Alternatives

Gilenya; Tysabri; Tecfidera; Aubagio; Lemtrada.

Clinical Notes

Daclizumab has a new and unique mechanism of action for the treatment of MS – it is a humanized monoclonal antibody that binds to the CD25 subunit of the high-affinity interleukin-2 (IL-2) receptor, to prevent signaling at the high-affinity IL-2 receptor while allowing increased IL-2 availability. Because IL-2 has a role in activating and regulating the immune system; CD25 antagonism may result in therapeutic benefit in MS. The exact mechanism by which daclizumab beta exerts therapeutic effects in MS is still unknown.

The efficacy of Zinbryta was established in two phase III, randomized, double-blind, controlled, multicenter, multinational pivotal studies in patients with relapsing MS.

DECIDE [n = 1,841], compared Zinbryta 150 mg SC once every 4 weeks with Avonex (interferon beta-1a intramuscular [IM] injection) 30 mcg IM once weekly for up to 3 years. The annualized relapse rate was 0.216 compared with 0.393 among patients given Zinbryta and Avonex, respectively, a 45% relative reduction. The proportion of patients experiencing confirmed disability progression was not statistically different among the agents.

The SELECT trial compared Zinbryta 150 mg SC every 4 weeks to placebo for 52 weeks [n = 412]. The annualized relapse rate was 0.211 for patients given Zinbryta compared with 0.458 among patients given placebo, a 54% relative reduction. Zinbryta also led to a 57% relative risk reduction in the proportion of patients with 12-week confirmed disability progression.

The common side effects associated with Zinbryta were nasopharyngitis (25%), upper respiratory tract infection (17%), rash (11%), influenza (9%), dermatitis (9%), oropharyngeal pain (8%), bronchitis (7%), eczema (5%) and lymphadenopathy (5%) in the DECIDE trial. Additionally, depression-related events were more common in the Zinbryta group (10%) than in the Avonex group (8%), an agent that has been associated with this side effect. Zinbryta has a boxed warning for hepatic injury, including autoimmune hepatitis and other immune-mediated disorder. It is contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

Place in Therapy

Canadian recommendations for treatment of RRMS currently list interferons and glatiramer acetate as first line of therapy – they are shown to have modest efficacy, and long-term safety has not raised concerns. Gilenya (fingolimod) and Tysabri (natalizumab) are both listed as second-line agents as they are more efficacious and present manageable adverse events. Lastly, third line options include Lemtrada (alemtuzumab) and mitoxantrone.

Zinbryta is a new alternative for patients with relapsing forms of MS who have not achieved adequate responses with other more established agents. Its subcutaneous administration is advantageous for patients who may self-administer the drug, in comparison with IV agents, who are often used as second or third-line agents.

Due to the risks associated with Zinbryta, it is only available in Canada through a controlled distribution program (Biogen ONE® Support Program). Only prescribers and pharmacies registered with the program are able to prescribe and dispense Zinbryta. Additionally, this drug can only be dispensed to patients who are registered with the Biogen One® Support Program – this program includes monthly monitoring and assessment of liver enzymes, prior to the next dose.

Comparative Pricing

Drug	Estimated Annual Cost
Zinbryta	$27,700
Copaxone 20mg/ml	$17,200
Copaxone 40mg/ml	$16,200
Avonex 30mcg/0.5ml	$23,250
Rebif 44mcg/0.5ml	$26,300
Tecfidera 240mg cap	$26,000
Aubagio 14mg tab	$21,500
Gilenya 0.5mg cap	$32,800
Lemtrada 12MG INJ	$30,000 - $50,000
Tysabri 300mg/15ml INJ	$ 44,100

Impact / Plan Management Suggestions

Intermediate impact; cost-shift from other second-line or third-line RRMS treatment options.

Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the January to March 2017 DEC Meetings

FIRST TIME GENERICS

First Time Generic Drugs (Notices of Compliance (NOCs) from November 30, 2016 to February 24, 2017)

Generic Name	Reference Drug (Brand)	Rank by ingredient cost in 2016	Manufacturer	Route of Administration	Approved Indications/ Comments
naproxen/ escitalopram	Vimovo	71	Mylan Pharmaceuticals ULC	Oral	osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS), decrease the risk of NSAID-associated gastric ulcers
desvenlafaxine	Pristiq	33	GenMed, a Division of Pfizer Canada Inc.	Oral	depressive disorder

NEW DRUGS AND PRODUCT LINE EXTENSIONS

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from November 30, 2016 to February 24, 2017)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Fycompa	perampanel	Eisai Ltd.	Oral Suspension	New formulation	New oral suspension formulation intended for use by those individuals unable to swallow tablets.
Kyprolis	carfilzomib	Amgen Canada Inc.	Intravenous injection	New strengths	10mg/vial and 30mg/vial added to currently available 60mg/vial has the potential to reduce drug waste and cost.
Omnitrope	somatropin	Sandoz Canada Inc.	Subcutaneous injection	New Strength	new 15mg/1.5ml strength
Fiasp	insulin aspart	Novo Nordisk Canada Inc.	Subcutaneous injection	New Brand, New Formulation	New faster-acting insulin aspart formulation developed to provide more physiological insulin response.
Dysport Aesthetic Dysport Therapeutic	abobotulinumtoxinA	Ipsen Biopharm Ltd.	Intramuscular injection	New brand, New indications, New strength	New brands to distinguish between cosmetic uses for treatment of glabellar lines (Dysport Aesthetic) and new therapeutic uses for treatment of cervical dystonia and focal spasticity (Dysport Therapeutic), with a new 500 Unit strength to accommodate these.

(continued next page)

EXPRESS SCRIPTS®

NEW DRUGS AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from November 30, 2016 to February 24, 2017)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Ilaris	canakinumab	Novartis Pharmaceuticals Canada Inc.	Subcutaneous injection	New indications, New dosage form	Treatment for Familial Mediterranean Fever (FMF), Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD). New dosage form: solution for injection.
Glatect	glatiramer acetate	Pharmascience Inc.	Subcutaneous injection	New Subsequent Entry Non Biologic Complex Drug	Lower-cost alternative to Copaxone for the treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS)
Gazyva	obinutuzumab	Hoffmann La Roche Ltd.	Intravenous injection	New indication	Treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen.
Kyleena	levonorgestrel releasing IUS	Bayer Inc.	Intrauterine system	New brand and strength	Kyleena (levonorgestrel-releasing intrauterine system) is indicated for conception control for up to 5 years similar to Mirena, and Jaydess
Otixal	ciprofloxacin-fluocinolone acetonide	Pediapharm Inc.	Otic Solution	New drug combination	For the treatment of patients 6 months and older with acute otitis media with tympanostomy tubes in pediatric patients.
Xolair	omalizumab	Novartis Pharmaceuticals Canada Inc.	Subcutaneous injection	New formulation	Prefilled syringes (PFS) should facilitate handling and administration of the drug, reducing the total injected volume (1ml per 150mg)
Stelara	ustekinumab	Janssen Inc.	Intravenous injection	New indication and new formulation	New Indication: Treatment of adult patients with moderately to severely active Crohn's disease using a single intravenous (IV) induction dose followed by subcutaneous therapy. Existing indications: plaque psoriasis, psoriatic arthritis.
Pazeo	olopatadine	Alcon Canada Inc.	Ophthalmic solution	New strength	Pazeo (olopatadine 0.7%) is a new option of treatment for patients suffering from allergic conjunctivitis
Glyxambi	linagliptin-empagliflozin	Boehringer Ingelheim (Canada) Ltd.	Tablet	New drug combination	Combination of the DPP-4 inhibitor, linagliptin, with the SGLT2 inhibitor, empagliflozin, for type 2 diabetes mellitus (T2DM).

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NEW DRUGS AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from November 30, 2016 to February 24, 2017)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Orfadin	nitisinone	Swedish Orphan Biovitrum AB (publ)	Capsule	New Brand	Treatment of patients with hereditary tyrosinemia type 1 (HT-1), it is the third nitisinone product to be approved by Health Canada
Repatha	evolocumab	Amgen Canada Inc.	Automated mini-doser (AMD) with prefilled cartridge for subcutaneous injection	New strength, New dosage form	The new dosage form and strength allows for easier administration of once-monthly dosing: use of one AMD (3.5ml) delivers 420mg.
Revlimid	lenalidomide	Celgene Inc.	Capsule	New strength, New indication.	Treatment of patients with transplant non-eligible newly diagnosed multiple myeloma (TNE NDMM); new strength of 2.5mg permits easier dose titration.
Odefsey	emtricitabine/ rilpivirine/ tenofovir alafenamide	Gilead Sciences Canada Inc.	Tablet	New drug combination	A fixed-dose, single tablet regimen of the antiviral drugs emtricitabine, rilpivirine, and tenofovir alafenamide for adults infected with HIV-1. Similar to Complera, with tenofovir disoproxil fumarate replaced by tenofovir alafenamide.
Cuvitru	immune globulin (human)	Baxalta Canada Corp.	Subcutaneous injection	New brand	Cuvitru is an alternate brand product to Hizentra
Lupron Depot	leuprolide acetate	Abbvie Corp.	Intramuscular injection	New indication	Indicated for the preoperative hematologic improvement in women of reproductive age with anemia caused by uterine leiomyomata (uterine fibroids) for up to three months.
Imbruvica	ibrutinib	Janssen Inc.	Capsule	New Indication	indicated in combination with Treanda (bendamustine) and Rituxan (rituximab) for the treatment of patients with CLL who have received at least one prior therapy

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