Health Newsflash

A Quarterly Publication

New Drugs Reviewed at the July to September 2015 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.

NOTEWORTHY NEW DRUGS

Cyramza™ (ramucirumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02443850 – 10mg/ml	Eli Lilly Canada Inc.	10:00.00 – Antineoplastic Agents

Indication(s)

Cyramza (ramucirumab) as a single agent or in combination with paclitaxel is indicated for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior platinum and fluoropyrimidine chemotherapy.

Dose

Cyramza in combination with paclitaxel

The recommended dose of ramucirumab is 8 mg/kg on days 1 and 15 of a 28-day cycle, prior to paclitaxel infusion. The recommended dose of paclitaxel is 80 mg/m^2 administered by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28-day cycle.

Cyramza as a single agent

The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks.

Therapeutic Alternatives

Other cytotoxic chemotherapy agents – different from those used in first-line treatment

Clinical Notes

Cyramza (ramucirumab (also known as IMC-1121B and LY3009806)) is a recombinant human IgG 1 kappa monoclonal antibody that specifically binds to the extracellular domain of the human vascular endothelial growth factor receptor-2 (VEGFR-2). Ramucirumab effectively blocks the interaction of VEGFR-2 with its ligands, VEGF-A, VEGF-C, and VEGF-D, resulting in inhibition of VEGF-stimulated activation of both VEGFR-2 and downstream signaling pathways.

This approval was based on the results of two phase 3 studies. In both trials, treatment was continued until disease progression or unacceptable toxicity. Patients in both trials had good performance status (ECOG ≤ 1). The RAINBOW trial demonstrated the effectiveness of adding Cyramza to second-line chemotherapy of paclitaxel compared to paclitaxel alone.
Median overall survival (OS) was longer in the ramucirumab group (9.6 months vs. 7.4 months).

(continued next page)

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Median progression-free survival (PFS) was longer in the ramucirumab + paclitaxel group than in the placebo + paclitaxel group (4.4 months vs. 2.9 months). Median duration of treatment was 18.0 weeks (IQR 10.0 – 31.1) in the ramucirumab + paclitaxel group vs. 12.0 weeks (6.4 – 20.0) in the placebo + paclitaxel group.

For those whom paclitaxel therapy is inappropriate, the REGARD trial demonstrated the benefit of Cyramza monotherapy over best supportive care. Median OS was 5.2 months in patients receiving ramucirumab vs. 3.8 months in patients receiving placebo. Median PFS was 2.1 months in patients receiving ramucirumab vs. 1.3 months in patients receiving placebo. Median duration of treatment was 8 weeks (IQR: 6-16) in the ramucirumab group vs. 6 weeks (4-8) in the placebo group.

Cyramza has also demonstrated benefits in other forms of cancer in other phase 3 trials including: non-small-cell lung cancer (NSCLC; REVEL trial, progression on platinum-based therapy); metastatic colorectal carcinoma (mCRC; RAISE trial, progression during or after first-line therapy). Other trials for other cancers are currently in progress.

Place in Therapy

Cyramza fills an unmet need in patients with gastric cancer or gastro-esophageal junction adenocarcinoma who have progressed on first-line chemotherapy. Due to ongoing trials, the full place in therapy for Cyramza has yet to be determined.

Pricing

Drug	Unit Price – single-use 10ml vials	Cost per cycle
Cyramza	$85	$10,200*

*based on 70kg patient, no dose sharing.

Impact

High impact – the only alternatives include continued “palliative” chemotherapy agents that have not been used by the patient before.

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Daklinza™ (daclatasvir)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02444747 – 30mg 02444755 – 60mg	Bristol-Myers Squibb Canada	08:18.40 – HCV Antivirals

Indication(s)

Daklinza (daclatasvir) is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adult patients with hepatitis C virus (HCV) genotypes 1, 2, or 3 and compensated liver disease, including cirrhosis. [NOC/c]

Dose

The recommended dose of Daklinza is 60 mg, taken orally, once daily with or without food. Dosage modification is required in case of potential drug-drug interactions with strong inhibitors or moderate inducers of CYP3A4 in a decrement or an increment of 30mg, respectively. It is anticipated that dose adjustment to 30mg once daily or 90mg once daily will occur in <2% of patients, based on the European experience.

Clinical Notes

Hepatitis C is a virus that infects the liver and is transmitted through direct contact with infected blood and blood products. Up to 90% of those infected with hepatitis C will not spontaneously clear the virus and will become chronically infected. According to the World Health Organization, left untreated up to 20% of people with chronic hepatitis C will develop cirrhosis; of those, up to 25% may progress to liver cancer. An estimated 350,000 to 400,000 people in Canada are chronically infected with HCV, but about 21% of those people are unaware and are undiagnosed. There are six different genotypes of HCV. In Canada, genotypes 1, 2 and 3 account for 64%, 14% and 20% of hepatitis C infections respectively.

Daklinza is a potent, pan-genotypic NS5A replication complex inhibitor (*in vitro*) that has been approved for use in combination with sofosbuvir (marketed in Canada by Gilead Sciences Canada Inc. as Sovaldi) as an all-oral, once-daily regimen.

Place in Therapy

Daklinza appears to offer a cost-effective treatment for genotype 3 infection in individuals without cirrhosis.

Comparative Pricing

Drug Regimen	Duration of treatment	Estimated treatment cost
Daklinza 30-90mg once daily + Sovaldi 400mg once daily	12 weeks	$96,000-$134,000
Sovaldi 400mg once daily + Ibavyr 1000-1200mg daily*	24 weeks	$122,000-$124,000

*weight-based ribavirin dosing – 1000mg if body weight < 75kg; 1200mg if body weight ≥ 75kg.

Impact

High impact due to high treatment cost, but potential cost savings in selected patient populations.

Eperzan™ (albiglutide)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02443635 – 30mg/0.5ml 02443643 – 50mg/0.5ml	GlaxoSmithKline Inc.	68:20.06 – Incretin mimetics

Indication(s)

Eperzan™ is indicated for once-weekly administration for the treatment of adults with type 2 diabetes mellitus, as an adjunct to diet and exercise to improve glycemic control

- as monotherapy in patients inadequately controlled by diet, exercise and when metformin is inappropriate due to contraindication or intolerance.
- in combination with one of the following therapeutic options in patients who have not achieved adequate glycemic control:
  - metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control
  - metformin and sulfonylurea, when diet and exercise plus dual therapy with metformin and sulfonylurea do not achieve adequate glycemic control
  - basal insulin with oral antidiabetic therapies, when diet and exercise plus basal insulin with oral antidiabetic therapies do not achieve adequate glycemic control

Dose

The recommended dose of Eperzan is 30 mg once weekly, administered subcutaneously. The dose may be increased to 50 mg once weekly based on individual glycaemic response.

Therapeutic Alternatives

Byetta (exenatide), Victoza (liraglutide)

Clinical Notes

Albiglutide is an agonist of the GLP-1 receptor and augments glucose-dependent insulin secretion. Albiglutide also slows gastric emptying. Albiglutide, a long-acting form of GLP-1, consists of recombinant GLP-1 genetically fused to human albumin. Similar to other GLP-1 receptor agonists, gastrointestinal adverse events were common. Hypoglycemia was the most common AE in albiglutide clinical trials with the highest rates amongst those concurrently using a sulfonylurea or insulin. Pancreatitis was also reported in numerically higher rates in albiglutide recipients in clinical trials.

Place in Therapy

Eperzan is the third GLP-1 receptor agonist to be approved in Canada. Its advantage is that it can be administered once weekly which may improve treatment adherence; however, it may have inferior blood glucose lowering effect than Victoza.

Pricing

Drug	Estimated annual cost
Eperzan	Price not available
Victoza	$2,100-$3,200
Byetta	$1,800

Impact

Insufficient information.

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Ofev™ (nintedanib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Capsule	02443066 – 100mg 02443074 – 150mg	Boehringer Ingelheim (Canada) Ltd.	48:92.00 – Respiratory Agents, Miscellaneous

Indication(s)

Ofev (nintedanib) is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

Dose

The recommended dose of Ofev is 150 mg twice daily administered approximately 12 hours apart.

Therapeutic Alternatives

Esbriet (pirfenidone)

Clinical Notes

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown aetiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency. It affects an estimated 30,000 Canadians, with a projected 5,000 deaths each year.

The active substance of Ofev is nintedanib, a tyrosine kinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and ß) and fibroblast growth factor receptors (FGFR 1-3) kinase activity crucial for the proliferation and migration of lung fibroblasts cells, and eventually inhibiting lung fibrosis.

The benefits with Ofev are its ability to reduce the rate of deterioration of lung function measured as decline of absolute volume of Forced Vital Capacity (FVC) in patients with idiopathic pulmonary fibrosis. It is noted that demonstration of this effect in the two pivotal clinical studies showed a clear and consistent benefit in reducing the decline of FVC by approximately 94 mL/year and 125 mL/year respectively.

A recent network meta-analysis appears to show a slight level of superiority of Ofev over Esbriet; although such indirect comparisons need to be taken with caution.

Place in Therapy

Ofev becomes the second drug available for the treatment of IPF which may slow progression of the disease. Ofev occupies a similar place in therapy as Esbriet. As noted above, there is currently little data to guide preference or potential sequencing of therapy.

Pricing

Drug	Annual cost
Ofev	$42,000
Esbriet	$45,000

Impact

High impact that may be mitigated by a cost-shift from similarly high-cost Esbriet.

Plegridy™ (peginterferon beta-1a)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02444372 – 63mcg/0.5ml 02444380 – 94mcg/0.5ml **02444399 – 125mcg/0.5ml** **02444402 – 63/94mcg/0.5ml (Starter Pack)** Only DINs in **bold** will be marketed	Biogen Idec Canada Inc.	92:20.00 – Immunomodulatory Agents

Indication(s)

Plegridy (peginterferon beta-1a) is indicated for treatment of relapsing remitting multiple sclerosis (RRMS) for adult patients

- to reduce the frequency of clinical exacerbations
- to slow the progression of disability.

Dose

The recommended dosage is 125 micrograms injected subcutaneously every 2 weeks. Medication comes in a prefilled syringe and dose needs to be titrated. Dose 1 on Day 0: 63 micrograms, Dose 2 on Day 14: 94 micrograms, Dose 3 on Day 28: 125 micrograms.

Therapeutic Alternatives

Betaseron, Rebif, Avonex, Copaxone, Aubagio, Tecfidera

Clinical Notes

The underlying cause of MS is currently unknown, but it is thought that a complex relationship between genetic and environmental factors, resulting in an autoimmune reaction against myelin cells coating the axons of neurons. This leads to inflammation and demyelination resulting in neuron axonal injury and loss of neural signal transmission. The exact mechanism of action of peginterferon beta-1a in patients with multiple sclerosis is unknown, but it is believed to reduce the inflammatory process involved in MS. Interferons are considered to be first line for the treatment of RRMS which is the most common form of MS. Plegridy is the pegylated formulation of interferon beta-1a. Pegylation provides a longer circulating half-life than the current first-line injectable, reducing the number of injections needed by a patient and decreasing the flu like side effects common with interferon beta-1a.

Place in Therapy

Pegylated interferon beta-1a treatment significantly reduced the annualized relapse rate compared with placebo (26% vs 40%; relative reduction of 36%) in a randomized trial in adults with relapsing/remitting multiple sclerosis (N=1012). At week 48, significantly fewer patients treated with pegylated interferon beta-1a had experienced a relapse (19% vs 29%), resulting in a 39% relative risk reduction for relapse.

Comparative Pricing

Drug	Unit Price	Estimated monthly cost
Plegridy	$876	$1,750
Avonex	$460	$1,850
Rebif	$142	$1,700
Betaseron	$120	$1,790

Impact

Minimal impact – cost shift from similarly priced alternatives.

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Strensiq™ (asfotase alfa)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02444607 – 12mg/0.3ml 02444615 – 18mg/0.45ml 02444623 – 28mg/0.7ml 02444631 – 40mg/1ml 02444658 – 80mg/0.8ml	Alexion Pharma International Sàrl	44:00.00 – Enzymes

Indication(s)

Strensiq (asfotase alfa) is indicated as enzyme replacement therapy for patients with confirmed diagnosis of paediatric-onset hypophosphatasia. [Conditional marketing approval, NOC/c]

Dose

Recommended dosage regimen of Strensiq is 2 mg/kg of body weight administered subcutaneously three times per week, or a dosage regimen of 1 mg/kg of body weight administered six times per week. The maximum volume of subcutaneous injection is 1 mL per injection.

Therapeutic Alternatives

None

Clinical Notes

Strensiq is asfotase alfa, a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein. Asfotase alfa is an enzyme replacement therapy intended to supplement tissue-nonspecific alkaline phosphatase activity. It is thought to exert its beneficial effects by promoting mineralisation of the skeleton in patients with paediatric-onset hypophosphatasia.

The benefit of exposure to Strensiq is an improvement in skeletal structure, as demonstrated by x-ray appearance of joints, by histological appearance of bone biopsy material and by apparent catch-up height-gain seen in some patients. The most common side effects are injection site reactions and injection-associated adverse reactions of mostly non-serious character and mild to moderate intensity.

Hypophosphatasia (HPP) is a rare, heritable form of rickets or osteomalacia with a live-birth incidence for the severe forms considered to be 1:100,000 in the general population. Prevalence is higher in certain populations, such as 1 per 2,500 births in Canadian Mennonites. This inborn-error-of-metabolism is caused by loss-of-function mutation(s) in the chromosome 1 liver/bone/kidney alkaline phosphatase gene (*ALPL*) that encodes the tissue-nonspecific isozyme of alkaline phosphatase (TNAP; also referred to as liver/bone/kidney type AP). The clinical severity of HPP varies greatly. The disease can be classified according to patient age when the first signs and symptoms manifest i.e., perinatal, infantile, childhood, and adult HPP. Additional clinical forms include odonto-HPP where there are only dental manifestations and prenatal benign-HPP. The severity of HPP ranges from total absence of bone mineralization and stillbirth to only dental problems with no bone manifestations.

Place in Therapy

Strensiq is the first enzyme replacement therapy available for the rare disease, HPP which has demonstrated improvements in skeletal radiographs and improved pulmonary and physical function in infants and young children with life-threatening HPP.

Comparative Pricing

Strensiq	Unit Price	Annual Cost
12mg/vial	N/A	$600,000* +
18mg/vial	$1,800	
28mg/vial	$2,900	
40mg/vial	$4,100	
80mg/vial	$8,200	

*assumption: 5-year-old child weighing 18kg (40 lbs.); since dose is weight-based cost will increase as patient grows.

Impact

High impact.

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FIRST TIME GENERICS

First Time Generic Drugs (Notices of Compliance (NOCs) from May 20, 2015 to August 19, 2015)

Generic Name	Reference Drug (Brand)	Rank by ingredient cost in 2014	Manufacturer	Route of Administration	Approved Indications/ Comments
pantoprazole magnesium	Tecta	48	Mylan Pharmaceuticals ULC	Oral	For treatment of conditions where a reduction of gastric acid secretion is required.
ziprasidone hydrochloride	Zeldox	507	GenMed, a division of Pfizer Canada Inc.	Oral	For the treatment of: • Schizophrenia and related disorders • Acute manic or mixed episodes associated with bipolar disorder
Indayo – levonorgestrel / ethinyl estradiol	Seasonale	244	Famy Care Ltd.	Oral	Contraception
dextroamphetamine sulfate	Dexedrine	277	Apotex Inc.	Oral	Narcolepsy Attention Deficit Hyperactivity Disorder (ADHD)
naltrexone	ReVia	599	Apotex Inc.	Oral	Opioid dependency disorder Alcohol dependency disorder
solifenacin	Vesicare	176	Teva Canada Ltd.	Oral	Overactive bladder
tobramycin inhalation solution	Tobi Inhalation Solution	261	Sandoz Canada Inc.	Inhalation	For management of cystic fibrosis patients with chronic Pseudomonas aeruginosa infections.

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NEW DRUG AND PRODUCT LINE EXTENSIONS

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from May 20, 2015 to August 19, 2015)

Band name	Chemical name	Manufacturer	Dosage form	New Drug or Type of Line Extension	Specifics/Comments
Movantik	naloxegol oxalate	AstraZeneca Canada Inc.	Tablet	New drug	For opioid induced constipation.
Inspiolto Respimat	olodaterol / tiotropium	Boehringer-Ingelheim (Canada) Ltd.	Metered-dose inhaler	New drug combination	Combination long-acting muscarinic antagonist (LAMA) and long-acting beta 2-adrenergic agonist (LABA) indicated for COPD.
Belkyra	deoxycholic acid	Kythera Biopharmaceuticals Inc.	Subcutaneous injection	New drug	Indicated for the cosmetic improvement in appearance due to submental (double-chin) fat in adults.
Jardiance	empagliflozin	Boehringer-Ingelheim (Canada) Ltd.	Tablet	New drug	This is the third SGLT2 inhibitor to become available on the Canadian market for treatment of type 2 diabetes mellitus.
MifeGymiso	mifepristone / misoprostol	Linepharma International Ltd.	Oral & Buccal Tablets	New drug combination	For first-trimester medical termination of pregnancy.
Viibryd	vilazodone hydrochloride	Forest Laboratories Canada Inc.	Tablet	New drug	New class of drug for the treatment of major depressive disorder.
Varithena	polidocanol	Provensis Ltd.	Intravenous foam injection	New drug	Sclerosing agent for the treatment of varicose veins.
Otezla	apremilast	Celgene Inc.	Tablet	New indication	For treatment of active psoriatic arthritis. Previously indicated for moderate to severe plaque psoriasis.
Quinsair	levofloxacin	Tripex Pharmceuticals LLC	Inhalation solution	New brand, new dosage form	Indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis. Quinsair is an alternative to Tobi inhalation solution/Tobi Podhaler.
Kalydeco	ivacaftor	Vertex Pharmaceuticals (Canada) Inc.	Oral Granules	New dosage form; new indication	Extension of use to pediatric patients 2 years of age and older who have one of the following mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or G970R. Previously only indicated for 6 years and older.

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NEW DRUG AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from May 20, 2015 to August 19, 2015)

Band name	Chemical name	Manufacturer	Dosage form	New Drug or Type of Line Extension	Specifics/Comments
Spiriva Respimat	tiotropium bromide	Boehringer Ingelheim (Canada) Ltd.	Soft mist inhaler	New indication	New indication for use as add-on maintenance bronchodilator treatment in adult patients with asthma who remain symptomatic on a combination of long-acting beta agonist and high-dose inhaled corticosteroid therapy and who experienced one or more severe exacerbations in the previous year. Previously indicated for maintenance bronchodilator therapy in patients with chronic obstructive respiratory disease (COPD).
VariZIG	varicella zoster immune globulin, human	Cangene Corp.	Intramuscular injection	New formulation	Now formulated as a solution rather than as a lyophilized powder.
Yasmin Plus	drospirenone / ethinyl estradiol / levomefolate	Bayer Inc.	Tablet	New strength; New brand	Brand extension of Yasmin with the addition of levomefolate.
Xarelto Starter Pack	rivaroxaban	Bayer Inc.	Tablet	New strength	Starter pack allows initiation of therapy based on starting regimen used in the EINSTEIN clinical development program.
Menjugate	meningococcal group C oligosaccharide	Novartis Vaccines and Diagnostics Srl	Suspension for intramuscular injection	New formulation	Now formulated as a suspension rather than as a lyophilized powder.
Prevnar 13	13-valent pneumococcal conjugate vaccine	Pfizer Canada Inc.	Suspension for intramuscular injection	New indication	Extension of indication to adults (18 years and older).
Breo Ellipta	fluticasone furoate/ vilanterol	GlaxoSmithKline Inc.	Dry powder inhaler	New strength, New indication	New indication for maintenance treatment of asthma (previously only indicated for COPD); New strength: higher strength – 200/25mcg/dose – for asthma only
Gadovist 1.0	gadobutrol	Bayer Inc.	Intravenous injection	New indication	Extension of current indication to neonatal/pediatric population 0 to 23 months of age.
Imbruvica	ibrutinib	Janssen Inc.	Capsule	New indication	New indication for relapsed or refractory mantle cell lymphoma (MCL). [NOC/c] Previously indicated for chronic lymphocytic leukemia (CLL).

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