Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the July to September 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

Defitelio™ (defibrotide)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02465981 – 80mg/ml	Jazz Pharmaceuticals Ireland Ltd.	20:12.20 – Thrombolytic agents

Indication(s)

Defitelio is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT) therapy.

Dose

The recommended dose of Defitelio is 25 mg/kg/day administered as 6.25 mg/kg every 6 hours given as a 2-hour intravenous infusion. Dosing should be based on patient's baseline body weight, defined as the patient's weight prior to the preparative regimen for HSCT. Administer for a minimum of 21 days. If after 21 days, signs and symptoms of hepatic VOD have not resolved, continue Defitelio until resolution of VOD.

Clinical Notes

Hepatic sinusoidal obstruction syndrome is one of the most feared complications of allogeneic and autologous hematopoietic cell transplantation. It accounts for a significant fraction of transplant-related mortality and, in its severe form, is almost always fatal. It is characterized by abdominal pain, hepatomegaly, jaundice and signs of portal hypertension (ascites, edema, varices). The mechanism of injury in SOS is through to be damage to endothelial cells in the liver following apoptosis and extrusion into sinusoids, which then causes obstruction and congestion.

Defibrotide is a thrombolytic agent that increases plasmin enzymatic activity to hydrolyze fibrin clots. It reduces endothelial cell (EC) activation and increases EC-mediated fibrinolysis by increasing tissue plasminogen activator and thrombomodulin expression, as well as by decreasing von Willebrand factor and plasminogen activator inhibitor-1 expression.

Studies suggest that defibrotide therapy plus supportive care results in long-term survival in a third to half of patients.

Place in Therapy

Defibrotide is a new option of treatment for SOS to be added to supportive care, particularly for patients who present with severe disease, which has a very poor prognosis.

Impact

The use of this drug is expected be restricted to the hospital setting for acute care patients.

EXPRESS SCRIPTS®

Maviret™ (glecaprevir/pibrentasvir)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02467550 – 100/40mg	AbbVie Corp.	08:18.40 – HCV Antivirals

Indication(s)

Maviret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors.

Dose

The recommended oral dose of Maviret is three fixed-dose combination glecaprevir/pibrentasvir 100/40 mg tablets administered once daily with food without regard to fat or calorie content. No dose adjustment is possible. The duration of treatment is for 8, 12 or 16 weeks and depends on whether patients have liver cirrhosis (scarring of the liver) or whether they have received previous treatments with pegylated interferon and ribavirin, with or without sofosbuvir, or sofosbuvir and ribavirin.

Therapeutic Alternatives

Epclusa (sofosbuvir/velpatasvir; pan-genotypic); Vosevi (sofosbuvir/velpatasvir/voxilaprevir; DAA treatment experienced)

Clinical Notes

Maviret is a fixed-dose combination of two pan-genotypic, direct-acting antiviral agents (DAAs), glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle.

The benefits with Maviret are that it is highly effective against all genotypes of HCV and can be used in patients with severe renal impairment, including in those on dialysis.

The most common side effects are headache and fatigue.

There are six varieties (genotypes) of the hepatitis C virus and Maviret has been shown to be effective at clearing all genotypes from the blood. In 8 main studies involving over 2,300 patients with hepatitis C, 99% of non-cirrhotic patients with genotype 1, the most common HCV genotype, tested negative for the virus after 8 weeks of Maviret treatment and 97% cirrhotic patients were negative after 12 weeks. A negative test result means that the virus was not found. Results were similar for genotypes 2 and 4-6. The medicine's effectiveness in clearing genotype 3 was slightly lower than for other genotypes (95%).

Place in Therapy

Maviret is the one of the latest in a growing number of treatments available for individuals with chronic hepatitis C virus infection. It fills a treatment gap for individuals with renal dysfunction who have GT 2, 3, 5 and 6 disease for whom the only treatment alternatives are pegylated interferon + ribavirin. It also provides a treatment alternative for individuals with GT 1 and 4 disease to Zepatier. Maviret is a treatment alternative to Vosevi for treatment experienced individuals with GT 1 disease who have been previously treated with an HCV NS5A inhibitor or an NS3/4A inhibitor, but not both.

Comparative Pricing

Drug	Estimated cost per treatment
Maviret	$40,000 - $80,000
Epclusa	$63,300 - $126,600
Vosevi	$63,300

Impact

Intermediate impact – potential cost-shift from higher cost alternatives.

Ocrevus™ (ocrelizumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02467224 – 30 mg/ml	Hoffmann-La Roche Ltd.	92:20.00 – Immunomodulatory Agents

Indication(s)

Ocrevus (ocrelizumab) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

Dose

Initial dose: 300 mg intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion. Subsequent doses: single 600 mg intravenous infusion every 6 months.

Therapeutic Alternatives

Aubagio, Gilenya, Lemtrada, Tecfidera, Tysabri; Zinbryta

Clinical Notes

Ocrevus is believed to work in multiple sclerosis (MS) by binding to CD20, a cell surface antigen found on pre-B and mature B lymphocytes. After cell surface binding to B lymphocytes, Ocrevus leads to antibody-dependent cellular cytolysis as well as complement-mediated lysis.

The efficacy of Ocrevus in patients with RRMS was established in two identical, Phase III, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group trials (OPERA I and OPERA II) that used Rebif (interferon beta-1a for subcutaneous [SC] injection) 44 mcg SC three times a week (TIW) as an active comparator for up to 96 weeks. Approximately 25% of patients had not used disease-modifying MS therapy within 2 years prior to the studies.

In OPERA I (n = 821) and OPERA II (n = 835) the annualized relapse rates (ARR) at 96 weeks were lower with Ocrevus in both studies compared with those for Rebif (0.16 vs. 0.29; $P < 0.0001$ [representing a 46% and 47% lower rate with Ocrevus vs. Rebif, respectively]). In a pooled analysis there was a 40% risk reduction in the proportion of patients with 12-week confirmed disability progression with Ocrevus compared with Rebif (9.8% vs. 15.2%; $P = 0.0006$). Several magnetic resonance imaging (MRI) parameters were also more favourable with Ocrevus vs. Rebif (e.g., mean number of T1-gadolinium [Gd]-enhancing lesions).

The most common adverse events in patients with relapsing-remitting MS (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections (40% vs. 33%) and infusion reactions (34% vs. 10%). Ocrevus has warnings/precautions related to infusion reactions, infections, and malignancies.

Place in Therapy

Canadian recommendations for treatment of RRMS (Freedman 2013) 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.

Comparative Pricing

Drug	Estimated Annual Cost
Ocrevus	$32,600
Copaxone 20mg/ml	$17,135
Glatect 20mg/ml	$13,805
Copaxone 40mg/ml	$16,200
Avonex 30mcg/0.5ml	$23,300
Rebif 44mcg/0.5ml	$26,330
Tecfidera 240mg cap	$25,955
Aubagio 14mg tab	$21,445
Gilenya 0.5mg cap	$32,800
Lemtrada 12mg INJ	$30,000 - 50,000
Tysabri 300mg/15ml INJ	$44,200
Zinbryta 150mg INJ	$27,700

Impact

Moderate impact (cost-shift from other therapeutic alternatives).

Onivyde™ (irinotecan liposome)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02467135 – 4.3mg/ml	Baxalta Canada Corp.	10:00.00 – Antineoplastic agents

Indication(s)

Onivyde (irinotecan liposome for injection) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin in adult patients who have disease progression following gemcitabine-based therapy.

Dose

Administer Onivyde 70 mg/m^2 by intravenous infusion over 90 minutes, followed by leucovorin 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours, every 2 weeks.

Therapeutic Alternatives

Leucovorin+5-FU+irinotecan+oxaliplatin; Oxaliplatin+5-FU+leucovorin; Leucovorin +5-FU-oxaliplatin

Clinical Notes

Onivyde represents a novel encapsulated formulation of irinotecan, in a long-circulating liposome (lipid bilayer vesicle). This preparation allows irinotecan to remain in circulation for a longer duration compared with standard irinotecan, which increases drug uptake within tumor cells and conversion of the drug to its active form. Liposomal irinotecan is not interchangeable with conventional irinotecan.

Place in Therapy

As second-line therapy in the treatment of metastatic pancreatic adenocarcinoma, the National Comprehensive Cancer Network (NCCN) has listed liposomal irinotecan+leucovorin+5-FU as a Category 1 recommendation for patients who were previously treated with gemcitabine-based therapy.

Comparative Pricing

Drug	Estimated Cost
Onivyde 4.3mg/ml	Pricing not available
Camptosar 20mg/ml INJ	$240 / vial
Teva-Irinotecan 20mg/ml INJ	$210 / vial

Impact

The use of this drug is expected be restricted to the hospital setting for cancer chemotherapy patients.

Procysbi™ (mercaptamine bitartrate or cysteamine bitartrate)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Oral capsule	02464705 – 25mg 02464713 – 75mg	Horizon Pharma Ireland Ltd.	92:92.00 – Other Miscellaneous Therapeutic Agents

Indication(s)

Procysbi is indicated for the treatment of nephropathic cystinosis.

Dose

The recommended starting dosage of Procysbi for cysteamine-naïve patients is 0.2 to 0.3 grams/m^2 (body surface area) per day divided into two doses given every 12 hours. The usual recommended maintenance dose of Procysbi for cysteamine-naive patients is 1.30 grams/m^2 per day, divided into two equal doses given every 12 hours.

Therapeutic Alternatives

Cystagon (cysteamine)*

*Only available through the Health Canada Special Access Program (SAP)

Clinical Notes

Cystinosis is a very rare autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal. Nephropatic cystinosis is the most common form of cystinosis and is estimated to affect 1 of every 100,000 to 200,000 children. In Canada, there appears to be a higher incidence of this disease in the Saguenay-Lac-Saint-Jean region, in Quebec.

As a result of deficient or absent cystinosin, which normally transports cystine out of the lysosome, cystine accumulates and forms crystals in many tissues, including the kidneys, liver, bone marrow, pancreas, muscle, rectal mucosa, brain and eye. Patients with cystinosis experience growth failure and rickets, and cystine deposits in the cornea cause photophobia. Over time, most organs are damaged. End-stage renal disease (ESRD) typically occurs before age 10 in the absence of treatment. Therapy of cystinosis consists of both amelioration of symptoms, the administration of cysteamine, and renal transplantation for those who progress to ESRD.

Procysbi reacts with cystine within the lysosome to convert it to cysteine and to a cysteine-cysteamine mixed disulfide, both of which can then exit the lysosome. Cysteamine should be started as soon as the diagnosis of cystinosis is confirmed. Early treatment with cysteamine preserves renal function, prevents hypothyroidism, reduces ocular discomfort and prevents visual impairment, and improves growth and survival.

The efficacy and safety of Procysbi in the treatment of nephropathic cystinosis was evaluated in two clinical trials. First, one randomized, multicenter, cross-over, pivotal study [n = 43] found that for the primary efficacy endpoint (per-protocol population), Procysbi taken every 12 hours (average daily dose of 1,513 mg/day) was non-inferior to Cystagon (cysteamine bitartrate immediate-release capsules, only available through SAP in Canada) taken every 6 hours (average daily dose of 1,801 mg/day) for maintenance of white blood cell (WBC) cystine levels below a specified threshold. Patients in this study were 6 years of age or older. A second long-term, open-label clinical trial evaluated the use of Procysbi in 60 patients aged 2 years or older. Long-term control of WBC cystine levels was maintained through the duration of the study (calculated up to 3.75 years). In total, 53 of the 62 patients (86%) in the age range of 2 to < 18 years were included in the two studies.

The most commonly reported adverse events (> 5%) in clinical trials were vomiting, abdominal pain/discomfort, headaches, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash.

Place in Therapy

Procysbi becomes the first product approved by Health Canada for treatment of nephropathic cystinosis. Treatment of patients with nephropathic cystinosis relies on cysteamine administration as soon as diagnosis is confirmed, to preserve renal function and improve life expectancy. Of note, Procysbi studies evaluated by Health Canada rely on WBC cystine levels, which are important to the disease course of nephropathic cystinosis, but not on clinical symptoms associated to the condition.

Comparative Pricing

Drug	Estimated Annual Cost
Procysbi	Price not available

Impact

Insufficient information.

Rydapt™ (midostaurin)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Oral capsule	02466236 – 25mg	Novartis Pharmaceuticals Canada Inc.	10:00.00 – Antineoplastic Agents

Indication(s)

Rydapt is indicated in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated acute myeloid leukemia (AML). A validated test is required to confirm the FLT3 mutation status of AML.

Dose

The recommended dose of Rydapt is 50 mg twice daily on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with cytarabine.

Patients may be given up to 2 cycles of induction therapy with cytarabine and daunorubicin if complete remission is not observed at the end of the first induction cycle. Each induction cycle is a minimum of 24 days in duration. Patients who have residual AML after a second induction cycle should be discontinued from Rydapt treatment.

Patients in complete remission after induction therapy should be given up to 4 cycles of consolidation therapy with cytarabine. Each consolidation cycle is a minimum of 28 days in duration and should begin within two weeks following hematologic recovery (ANC ≥ 1000/μL and platelet count ≥ 100,000/μL) but not sooner than 28 days from the beginning of the previous cycle.

Therapeutic Alternatives

Cytosar (cytarabine) + Cerubidine (daunorubicin); Cytosar (cytarabine) + Idamycin (idarubicine).

Clinical Notes

In 2016, approximately 5,900 new cases of leukemia were diagnosed in Canada. Of these, 24% present with AML, a rapidly-progressing cancer of myeloid stem cells. The average age at the time of AML diagnosis is 67. The age-standardized five-year survival rate for leukemia is 58% for males and 59% for females. This hematologic malignancy has seen limited treatment advances in the last decades.

Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene producing internal transmembrane duplications (FLT3-ITD) or changes in the activating loop of the kinase domain (FLT3-TKD) are found in approximately one-third of adults with AML. These mutations are associated with decreased response and overall survival in patients.

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 receptor signaling and induces cell cycle arrest and apoptosis in leukemic cells expressing internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutant receptors or overexpressing wild type receptors. Midostaurin inhibits both the wild type and D816V mutant KIT, leading to interference with the aberrant signaling of KIT and inhibits mast cell proliferation and survival, and histamine release.

The efficacy of Rydapt in FLT3-mutated AML was established in RATIFY, a Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal study. RATIFY included 717 adults 18 to 60 years of age with FLT3-mutated AML, and demonstrated that Rydapt + standard intravenous (IV) chemotherapy was superior to placebo plus standard IV chemotherapy in overall survival (OS) [hazard ratio {HR} 0.77; 95% confidence interval {CI}: 0.63, 0.95; P = 0.016]. Rydapt reduced the risk of death by 23%. The most common Grade 3/4 adverse events (AEs) in patients treated with Rydapt + chemotherapy in the study (incidence ≥ 10%) were febrile neutropenia, device-related infection and mucositis. The rate of drug discontinuation due to AEs in the AML study was 9% in the Rydapt + chemotherapy arm and 6% in the placebo + chemotherapy arm.

Place in Therapy

Rydapt (midostaurin) represents an additional therapy to standard chemotherapy protocol, for patients with FLT3-mutated AML, which carries a poorer prognosis. The NCCN guidelines have integrated the triple-therapy as an option for induction treatment of AML.

Comparative Pricing

Drug	Estimated cost per treatment
Rydapt	Price not available
Cytarabine 200mg/m^2 x 7 days + daunorubicin 60mg/m^2 x 3 days (based on 1.73m^2 BSA)	$1,900
Cytarabine 200mg/m^2 x 7 days + idarubicin 12mg/ m^2 x 3 days (based on 1.73m^2 BSA)	$2,800

Impact

Insufficient information.

Spinraza™ (nusinersen)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intrathecal injection	02465663 – 2.4mg/ml	Biogen Canada Inc.	92:92.00 – Other Miscellaneous Therapeutic Agents

Indication(s)

Spinraza (nusinersen) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).

Dose

The recommended dose is 12 mg (5 mL).

Loading doses

Initiate treatment with 4 loading doses. The first 3 loading doses should be administered at 14-day intervals (e.g., Day 0, Day 14, Day 28). The fourth loading dose should be administered approximately 30 days after the third loading dose (e.g., Day 63).

Maintenance doses

Following the fourth loading dose, a maintenance dose should be administered once every 4 months.

Therapeutic Alternatives

No therapeutic alternatives are available. Spinraza is the first disease-modifying therapy to become available for SMA. Prior to its availability, treatment has been supportive aimed at providing nutrition and respiratory assistance as needed, and treating or preventing complications of weakness.

Clinical Notes

Spinal muscular atrophy (SMA) is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, individuals with the most severe type of SMA can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing.

SMA is inherited in an autosomal recessive manner. Due to a loss of, or defect in, the SMN1 gene, people with SMA do not produce enough SMN protein, which is critical for the maintenance of motor neurons. The severity of SMA correlates with the amount of SMN protein. People with Type 1 SMA, the form that requires the most intensive and supportive care, produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. People with Type 2 and Type 3 SMA produce greater amounts of SMN protein and have less severe, but still life-altering forms of SMA. Type 4 SMA is a still milder, adult-onset form of the disease.

The incidence and prevalence of SMA has been difficult to determine. When examining all types of SMA together, in most cases a prevalence of around 1–2 per 100,000 persons is observed. Upon evaluation of all types of SMA combined yields an average incidence of around 8 per 100,000 live births (~1 in 12,000). Incidence tends to vary based on ethnicity ranging from 1 in 8,000 in Asians and Caucasians to 1 in 20,000 in black and Hispanic populations.

Spinraza is an antisense oligonucleotide (ASO) specifically designed to treat SMA, an autosomal recessive progressive neuromuscular disease, caused by mutations in the chromosome 5q. These mutations lead to loss of function of the survival motor neuron 1 (SMN1) gene, resulting in deficiency of SMN protein. The SMN2 gene also produces SMN protein but at low levels. In patients with SMA, fewer SMN2 gene copies are associated with earlier age of onset and increased severity of symptoms.

Spinraza binds to a specific site in the SMN2 pre-messenger ribonucleic acid (pre-mRNA) to increase the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts made, which can be translated into the functional full length SMN protein.

The efficacy of Spinraza was established in one, Phase III, unpublished, multicenter, multinational, randomized, double-blind, sham-procedure controlled trial called ENDEAR which involved symptomatic infants (n = 121) diagnosed with type 1 spinal muscular atrophy (median age at first treatment was 181 days). Due to favourable results in ENDEAR, the trial was stopped early.

- A planned interim efficacy analysis in the ENDEAR trial was conducted based on 82 patients who died, withdrew, or completed at least 183 days of treatment. A greater percentage of patients who received Spinraza achieved a motor milestone response (defined as improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam [HINE]) compared with patients given sham-procedure control (40% [n = 21/52] vs. 0% [n = 0/30], respectively) [P < 0.0001].
- Also, at this interim analysis, more patients given Spinraza vs. sham-procedure control (63% vs. 3%, respectively) achieved improvement from baseline of at least 4-points on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), which assesses motor skills.
- Other supportive data are available for Spinraza, mainly open-label, uncontrolled trials, some of which involved different disease types (types II or III) including symptomatic patients who were older (aged up to 15 years) as well as presymptomatic infants (age range at first dose, 8 days to 42 days).

The most common AEs (incidence ≥ 20% and at least 5% more frequently than in control) with Spinraza were lower respiratory tract infection (43%), upper respiratory tract infection (39%), and constipation (30%).

Place in Therapy

Spinraza is the only treatment available for this serious, genetic condition that leads to substantial disability for many patients and a vastly shortened lifespan in those with infantile-onset disease. The agent is indicated broadly for use among patients with various types of spinal muscular atrophy. In the ENDEAR pivotal study, which is not fully-published, substantial improvements in motor milestone responses were observed with Spinraza compared with sham-procedure control in infants with type 1 spinal muscular atrophy.

Comparative Pricing

Drug	Estimated Annual Cost
Spinraza	First year: $708,000 Subsequent years: $354,000

Impact

High impact. Although SMA is a rare disease, the ultra-high cost of Spinraza can have serious impacts on payers. Intrathecal administration of the drug can be a challenge in the outpatient setting.

Tresiba® (insulin degludec)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02467860 – 100 Unit/ml Penfill (Cartridge) 02467879 – 100 Unit/ml FlexTouch (Prefilled Pen) 02467887 – 200 Unit/ml FlexTouch (Prefilled Pen)	Novo Nordisk Canada Inc.	68:20.08 – Insulins

Indication(s)

Tresiba is indicated for once-daily treatment of adults with diabetes mellitus to improve glycemic control.

Dose

The dosage of Tresiba should be individualized and titrated under the supervision of a health care provider in accordance with the metabolic needs of the patient and the glycemic control target and with appropriate glucose monitoring.

Therapeutic Alternatives

Lantus, Basaglar, Toujeo (insulin glargine); Levemir (insulin detemir)

Clinical Notes

The active substance of Tresiba is insulin degludec, a basal insulin. Insulin degludec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin.

Tresiba has been studied in three main studies involving 1,578 patients with type 1 diabetes, where Tresiba (in combination with rapid-acting mealtime insulin) was compared with insulin glargine or insulin detemir (other long-acting insulins).

Six other main studies involving 4,076 patients with type 2 diabetes compared Tresiba with insulin glargine, insulin detemir or sitagliptin (a medicine taken by mouth for type 2 diabetes). Patients in these studies could also be given other diabetes medicines or rapid-acting insulin at mealtimes if needed. Another main study involving 177 patients with type 2 diabetes investigated the effectiveness of combining Tresiba and liraglutide (a GLP-1 receptor agonist).

The studies showed that Tresiba was at least as effective as other long acting insulins in controlling blood glucose levels in patients with type 1 and type 2 diabetes, and more effective than sitagliptin in patients with type 2 diabetes. Across the studies, the average reduction in HbA1c levels with Tresiba treatment was 0.6 percentage points in patients with type 1 diabetes and 1.2 points in patients with type 2 diabetes.

Tresiba has demonstrated glycemic (HbA1C reduction) non-inferiority to Lantus and Levemir as part of a basal-bolus regimen in patients with type 1 or type 2 diabetes and as part of a combination regimen with oral antidiabetic drugs (OADs) in patients with type 2 diabetes. Tresiba has also demonstrated superiority for HbA1C reduction to the oral agent Januvia in patients with type 2 diabetes as part of a combination regimen with other OADs. Overall rates of confirmed hypoglycemia appear similar between Tresiba, Lantus, and Levemir. Statistical differences in nocturnal confirmed hypoglycemia were noted in all three of the clinical trials in patients with type 1 diabetes and in two of the five pivotal trial comparing Tresiba with Lantus or Levemir in patients with type 2 diabetes. However, the clinical relevance of the statistical significance remains uncertain in light of overall low rates of hypoglycemia and small numeric differences. Tresiba produced generally similar weight gain to Lantus and Levemir in pivotal trials. Tresiba is available in a standard (U-100) and more concentrated formulation (U-200); the latter negates more than one injection in patients requiring larger insulin doses.

Place in Therapy

At this time Tresiba represents another effective basal insulin therapy in patients with diabetes who require use of basal insulin. The place in therapy will continue to evolve with clinical use and incorporation into clinical guidelines.

Comparative Pricing

Drug	Estimated Cost Per Unit
Tresiba	$0.0719
Basaglar	$0.0464
Lantus	$0.0619
Toujeo	$0.0587
Levemir	$0.0719

Impact

Minimal impact – cost-shift from similarly priced alternative; e.g., Levemir.

Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02467542 – 400/100/100mg	Gilead Sciences Canada, Inc.	08:18.40 – HCV Antivirals

Indication(s)

Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adult patients, without cirrhosis or with compensated cirrhosis, who have:

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor;
- genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

Dose

Vosevi is a single tablet regimen. No dosage adjustments are possible for Vosevi.

The recommended dose of Vosevi is one tablet of 400 mg/100 mg/100 mg sofosbuvir/velpatasvir/voxilaprevir, taken orally, once daily with food.

Therapeutic Alternatives

Maviret (glecaprevir/pibrentasvir, DAA treatment experienced, Genotype-1 only)

Clinical Notes

Vosevi is a fixed-dose combination of three direct-acting antivirals (DAA), sofosbuvir, velpatasvir and voxilaprevir. It will be available as film-coated tablets (containing 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir). The active metabolite of sofosbuvir is an inhibitor of the hepatitis C virus (HCV) NS5B RNA polymerase, velpatasvir targets the NS5A protein of the virus and voxilaprevir inhibits the non-structural protein NS3/4A protease; all these proteins are essential for viral replication.

The benefits with Vosevi are that it is highly effective against all genotypes of HCV and can be used in patients in whom prior treatment with other direct-acting antivirals has failed. The most common side effects are headache, diarrhoea and nausea.

The efficacy of Vosevi was established in two, randomized, Phase III pivotal trials in adults with chronic HCV of any genotype with or without compensated cirrhosis who did not have a sustained viral response (SVR) with a prior DAA-based regimen. POLARIS-1 was a placebo-controlled study that enrolled patients with prior NS5A experience. POLARIS-4 had an active comparison with Epclusa® (sofosbuvir/velpatasvir tablets) and enrolled patients who had previously been treated with any DAA regimen containing Sovaldi without an NS5A inhibitor.

- In POLARIS-1 (published) [n = 263], the overall rate of SVR measured 12 weeks after treatment completion (SVR12) in the Vosevi group was 96% (95% confidence interval [CI]: 93, 98), which was superior to the prespecified performance goal of 85% ($P < 0.001$).
- In POLARIS-4 (published) [n = 333], the overall rate of SVR12 was 98% (95% CI: 95, 99) among Vosevi-treated patients which was superior to the prespecified performance goal of 85% ($P < 0.001$). Among Epclusa-treated patients SVR12 was 90% (95% CI: 84, 94), which was not significantly superior to the prespecified performance goal of 85%. In patients with genotype 1a or genotype 3 infection, the rates of SVR12 were higher with Vosevi vs. Epclusa (98% vs. 89% and 96% vs. 85%, respectively). For genotypes 1b and 2 the rates of SVR12 for Vosevi and Epclusa were similarly high; no patients with genotype 4 enrolled in the Epclusa group and no patients with genotypes 5 or 6 were enrolled in either the Vosevi or Epclusa arm.

Place in Therapy

Vosevi is the first DAA indicated for the retreatment of patients with HCV who have previously been treated with an NS5A inhibitor and for patients with genotype 1a or 3 who have previously been treated with Sovaldi + a non-NS5A inhibitor. Vosevi has a niche indication for retreatment which broadly encompasses all currently recommended DAA therapies in patients with genotypes 1 through 6 without cirrhosis or with compensated cirrhosis. As a whole, the proportion of patients who fail the currently available DAAs is low. Although difficult to extrapolate, it is estimated approximately 7% of the entire treated HCV population will fail a currently available DAA. Therefore, while Vosevi does have a niche place in therapy for patients who have failed an NS5A inhibitor or a regimen containing Sovaldi + a non-NS5A inhibitor for some patients, it does not have a unique place in therapy overall for the broader treatment of HCV.

Comparative Pricing

Drug	Estimated Annual Cost
Vosevi	$63,300
Maviret	$60,000 - $80,000

Impact

Intermediate impact – niche place in therapy but similar cost to potential alternatives.

FIRST TIME GENERICS

First Time Generic Drugs (Notices of Compliance (NOCs) from May 31, 2017 to August 30, 2017)

Generic Name	Reference Drug (Brand)	Rank by ingredient cost in 2016	Manufacturer	Route of Administration	Approved Indications/ Comments
eplerenone	Inspra	574	Apotex Inc.	Oral	Reduce the risk of cardiovascular mortality and hospitalization for heart failure, and hypertension
doxylamine/ pyridoxine	Diclectin	116	Pharmascience Inc.	Oral	Management of nausea and vomiting of pregnancy
deferasirox	Exjade	263	Sandoz Canada Inc.	Oral	Management of chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older
acitretin	Soriatane	510	Taro Pharmaceuticals Inc.	Oral	Severe psoriasis and other disorders of keratinization.
benzoyl peroxide/ clindamycin	BenzaClin	149	Taro Pharmaceuticals Inc.	Topical	Topical treatment of moderate acne vulgaris
budesonide	Pulmicort Nebuamp	376	Teva Canada Ltd.	Inhalation	For patients with bronchial asthma
efavirenz-emtricitabine-tenofovir disoproxil fumarate	Atripla	143	Teva Canada Ltd.	Oral	Treatment of HIV-1 infection in adults
tenofovir disoproxil fumarate	Viread	87	Teva Canada Ltd.	Oral	Treatment of HIV or chronic hepatitis B for adults and adolescent patients

Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the July to September 2017 DEC Meetings

NEW DRUGS AND PRODUCT LINE EXTENSIONS

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from May 31, 2017 to August 30, 2017)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Adcetris	brentuximab vedotin	Seattle Genetics Inc.	Intravenous Injection	New indication	For the post-ASCT consolidation treatment of patients with Hodgkin lymphoma (HL).
Aermony Respiclick	fluticasone propionate	Teva Canada Ltd.	Inhaler	New brand	Lower cost alternative to but not interchangeable with Flovent.
Belbuca	buprenorphine HCl	Paladin Labs Inc.	Buccal Film	New dosage form	Treatment of chronic pain not responsive to other opioid treatment where buccal administration is an alternative to the transdermal patch.
BeneFIX	coagulation factor IX	Pfizer Canada Inc.	Powder for Solution	New strength	New strength of 1,500 Unit/vial.
Bortezomib for Injection	bortezomib	Pfizer Canada Inc.	Powder for Injection	New strength	New Strengths 2.5 mg/Vial, 3.5 mg/Vial.
Cimzia	certolizumab pegol	UCB Canada Inc.	Solution for Injection	New dosage form	New dosage form provides an easy to use injection delivery format.
Emend IV	fosaprepitant dimeglumine	Merck Canada Inc.	Intravenous injection	New indication	Prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy in both males and females – previously only indicated for use in females.
Esbriet	pirfenidone	Hoffmann-La Roche Ltd.	Tablets	New dosage form; new strength	The new dosage form is a film-coated tablet designed to be easier to swallow than the original capsule. The 801mg tablet can be taken three times per day instead of three capsules of the original strength.
Fibryna	fibrinogen (human)	Octapharma Canada Inc.	Intravenous Injection	New brand	Fibryna provides an alternative to RiaSTAP which is another human fibrinogen product.
Flebogamma	immune globulin (human)	Instituto Grifols S.A.	Intravenous injection	New brand	Flebogamma is a blood product and an alternate brand product to a variety of other immune globulins available.
Fraxiparine	nadroparin calcium	Aspen Pharmacare Canada Inc.	Subcutaneous/ Intravenous injection	New indication	Prophylaxis of thromboembolic disorders in high risk medical patients immobilised due to acute illness or hospitalised in an intensive care unit.

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NEW DRUGS AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from May 31, 2017 to August 30, 2017)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
FreeStyle Libre Flash Glucose Monitoring System	flash glucose monitoring	Abbott Diabetes Care Ltd.	Sensor	New device approval	Designed to replace self-monitoring of blood glucose (SMBG) testing for individuals with both Type 1 and Type 2 diabetes who require frequent testing or who may be at risk for hypoglycemia (especially nocturnal), are not candidates for continuous glucose monitoring (CGM).
Galexos	simeprevir	Janssen Inc.	Capsule	New indication	Treatment of chronic hepatitis C (CHC) in adults with compensated liver disease in combination with sofosbuvir (Sovaldi®) for genotype 4 disease.
Halaven	eribulin mesylate	Eisai Ltd.	Intravenous injection	New indication	New Indication is the treatment of adult patients with an unresectable advanced or metastatic liposarcoma subtype of soft tissue sarcoma.
Humira	adalimumab	AbbVie Corp.	Subcutaneous injection	New strength	New strength of 80mg/pre-filled syringe.
Influvac	influenza vaccine	BGP Pharma	Intramuscular injection	Expansion of indication	New Indication for the prevention of influenza infection caused by the specific strains contained in the vaccine, in adults and children from 3 years of age. Previously only indicated in adults.
Isentress HD	raltegravir potassium	Merck Canada Inc.	Tablet	New strength	New 600mg strength to be used as once-daily dosing instead of twice daily dosing which simplifies the dosing regimen and reduces the burden on the patient.
Keytruda	pembrolizumab	Merck Canada Inc.	Intravenous solution	New indication	First-line treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumour have high PD-L1 expression.
Latuda	lurasidone HCl	Sunovion Pharmaceuticals Canada Inc.	Tablet	New indication	Expanding the indication to adolescents (age 15-17) with schizophrenia.
Orkambi	lumacaftor / ivacaftor	Vertex Pharmaceuticals (Canada) Inc.	Tablet	New indication, New strength	New Indication for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; with a new strength of 100/125mg for patients age 6-11 years.

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NEW DRUGS AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from May 31, 2017 to August 30, 2017)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
pms-Fluoxetine	fluoxetine	Pharmascience Inc.	Capsule	New strength	New strength of 60mg capsule can be taken once per day instead of three of 20mg capsules once daily.
Praluent	alirocumab	Sanofi-aventis Canada Inc.	Subcutaneous injection	New dosage regimen	New dosing regimen of 300mg once every 4 weeks can be used for those individuals who prefer less frequent dosing.
Prolastin-C	alpha 1-proteinase inhibitor	Grifols Canada Ltd.	Intravenous solution	New indication	Indicated for chronic replacement therapy of individuals having congenital deficiency of alpha1-PI related to genotypes PiZZ, PiZ(null), Pi (null)(null), PiSZ or other deficiency causing alleles with clinically demonstrable emphysema.
Stivarga	regorafenib	Bayer Canada	Tablet	Modification to the indication	Potential treatment option for patients with metastatic colorectal cancer in 3rd line in both RAS-mutant* and wild-type tumors. (*previously KRAS).
Victoza	liraglutide	Novo Nordisk Canada Inc.	Subcutaneous injection	New indication	Victoza is indicated for once-daily administration for the treatment of adults with type 2 diabetes to improve glycemic control in combination with diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance.
Xalkori	crizotinib	Pfizer Canada Inc.	Capsule	Expansion to the indication	As monotherapy for use in patients with ROS1-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC, in addition to patients with ALK-positive mutations.

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