Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the April to June 2016 DEC Meetings

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

NEW DRUGS

Blexten™ (bilastine)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02454130 – 20mg	Aralez Pharmaceuticals Trading DAC	04:00.00 – Antihistamine drugs

Indication(s)

Blexten is indicated for the symptomatic relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older and for the relief of the symptoms associated with chronic spontaneous urticaria (CSU) (e.g. pruritus and hives) in patients 18 years of age and older.

Dose

The recommended daily dose is 20mg once daily.

Therapeutic Alternatives

Reactine (cetirizine)*,
Aerius (desloratadine)*,
Claritin (loratadine)*,
Allegra (fexofenadine)*

*generic available

Clinical Notes

Bilastine is a non-sedating second-generation H1 antihistamine. It shows moderate to high affinity for histamine H1-receptors (3 times higher than cetirizine) and no affinity for muscarinic, serotonergic, dopaminergic and noradrenergic receptors. Bilastine has limited distribution to the brain following oral administration. This minimizes the drug's impact on psychomotor performance (i.e., drowsiness and somnolence). A study evaluated the impairment effect of bilastine 20 to 40mg on 22 subjects. Bilastine did not produce any impairment on driving after single and repeated doses, while its comparator (hydroxyzine 50mg) did.

Various studies compared bilastine 20mg to cetirizine 10mg, levocetirizine 5mg or desloratadine 5mg and showed similar effectiveness in controlling symptoms of perennial allergic rhinitis and chronic spontaneous urticaria, as well as a comparable side effect profile.

Place in Therapy

Bilastine 20mg once daily is as efficacious as other non-sedating antihistamines in allergic rhinoconjunctivitis and chronic urticaria. It did not show any impact on psychomotor performance or driving, even at twice the therapeutic dose.

Bilastine enters the Canadian market as a prescription medication, while most of the other options of treatment available are over-the-counter – cetirizine 20mg tablet is the only other second-generation antihistamine still available through prescription. At this dose of cetirizine, somnolence rates of 23.9% are reported, which gives bilastine an advantage when selecting an option for treatment.

Comparative Pricing

Drug	Estimated Annual Cost
Bilastine 20mg once daily	Price not available
cetirizine 20mg once daily	$275
desloratadine 5mg once daily	$200
loratadine 10mg once daily	$230

Impact/Plan Management Suggestions

Insufficient information.

Brivlera™ (brivaracetam)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet, Oral solution, Injection	02452936 – 10mg tab 02452944 – 25mg tab 02452952 – 50mg tab 02452960 – 75mg tab 02452979 – 100mg tab 02452987 – 10mg/ml o/l 02452995 – 10mg/ml inj	UCB Canada Inc	28:12.92 – Miscellaneous Anticonvulsants

Indication(s)

Brivlera (brivaracetam) is indicated as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

Brivlera (brivaracetam) injection for intravenous use is an alternative when oral administration is temporarily not feasible.

Dose

The recommended starting dose is 50 mg twice daily (100 mg per day). Based on individual patient response and tolerability, the dose may be adjusted between 25 mg twice daily (50 mg per day) and 100 mg twice daily (200 mg per day). Brivlera is initiated at a therapeutic dose, which separates it from other antiepileptic drugs (AEDs), which need to be titrated.

Maximum recommended daily dose of Brivlera is 200 mg, administered in two equal doses.

Brivlera can be administered intravenously without further dilution. When switching to or from oral to intravenous administration of Brivlera, the total daily dose and frequency of administration should be maintained.

Therapeutic Alternatives

Keppra (levetiracetam)*, Vimpat (lacosamide), Fycompa (perampanel), Aptiom (eslicarbamazepine), and others

* Generics available

Clinical Notes

Brivaracetam is an analog of levetiracetam. The primary mechanism of brivaracetam appears to relate to its selective binding to the synaptic vesicle protein 2A (SV2A) in the brain. Brivaracetam is different from levetiracetam, the only other SV2A ligand by its selective, higher affinity (more than 30-fold) and differential interaction with the SV2A protein. The precise mechanism by which brivaracetam exerts its anticonvulsant activity has not been fully elucidated.

Despite a great number of treatment options available in epilepsy, 30 to 40% of patients do not achieve seizure control. The efficacy of brivaracetam as adjunctive therapy in partial-onset seizures was established in three fixed-dose, randomized, double-blind, placebo-controlled, multicenter studies which included a total of 1558 patients (1099 patients were exposed to brivaracetam and 459 patients received placebo). Patients had partial onset seizures with or without secondary generalization and were not adequately controlled with 1 to 2 concomitant antiepileptic drugs (AEDs). Clinical efficacy was shown in all three studies for doses of brivaracetam of 100mg/day, significantly reducing frequency of partial-onset seizures. Of note, data available for patients already on levetiracetam was non-conclusive.

Brivaracetam is generally well tolerated, having a comparable side-effect profile to other AEDs.

Place in Therapy

Brivlera joins multiple other AEDs indicated for adjunctive use in patients with partial-onset seizures. Brivlera has a similar mechanism of action to levetiracetam, which is available generically. Treatment of partial-onset seizures requires individualized treatment based on seizure type, disease severity, response to therapy, drug-drug interactions, and tolerability. At this time, Brivlera is considered a therapeutic alternative to the armamentarium of medications currently available that have been proven effective as adjunctive therapy in the treatment of partial-onset seizures.

Comparative Pricing

Drug Regimen	Estimated annual cost
Brivlera	$3,200
levetiracetam	$1,000-2,900
Vimpat	$1,900-$4,400
Fycompa	$3,700
Aptiom	$3,700-$7,700

Impact/Plan Management Suggestions

Minimal impact – cost shift from generally similarly priced alternatives. List similar to other AEDs used as adjunctive treatment of partial-onset seizures.

Ibrance™ (palbociclib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02453150 – 75mg 02453169 – 100mg 02453177 – 125mg	Pfizer Canada Inc.	10:00.00 – Antineoplastic Agents

Indication(s)

Indicated for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. [NOC/c – conditional approval pending results from a confirmatory Phase 3 trial]

Dose

The recommended dose of Ibrance is 125mg taken orally once daily for 21 consecutive days followed by 7 days off treatment – comprising a complete cycle of 28 days. It should be taken in combination with letrozole 2.5mg once daily given continuously.

Therapeutic Alternatives

Femara (letrozole)*; Aromasin (exemestane)*; Arimidex (anastrozole)*; Afinitor(everolimus) +Aromasin(exemestane)*; Faslodex (fulvestrant)

* Generics available

Clinical Notes

In 2015, 25,000 new cases of breast cancer were diagnosed (26% of all new cancer cases) in Canada. Literature indicates that 4.9% of Canadian patients present with metastatic disease at diagnosis. The yearly number of patients for whom Ibrance could be indicated (post-menopausal (82% of patients), ER+/HER- (72% of patients)) is estimated to be around 723.

Current options of treatment available for metastatic breast cancer ER+ are hormonal therapies in first-line, such as aromatase inhibitors or selective estrogen receptor modulators. If progression occurs on endocrine therapy, targeted therapy comprised of Afinitor+exemestane or selective estrogen receptor down-regulator such as fulvestrant are considered. Lastly, chemotherapy is available for most aggressive cases or if any further progression occurs – as chemotherapy produces a heavier side effect profile, palbociclib aims to lengthen time before it is required.

Palbociclib is a selective, reversible, small molecule inhibitor of cyclin-dependant kinases (CDK) 4 and 6. These kinases are engaged in a signaling pathway leading to cellular growth and proliferation. By inhibiting their action, palbociclib blocks cell cycle progression from G1 into S phase. Combining this mechanism with therapeutic withdrawal of estrogen further reduces tumor cell viability.

Following withdrawal of palbociclib, affected cells do not resume proliferation in the presence of anti-estrogens – thus supporting the dosing regimen of 3 weeks on, one week off of treatment. This schedule will allow for bone marrow cells to recover during the treatment-free week without impacting tumor efficacy.

A Phase 2 study (PALOMA-1) evaluated progression-free survival (PFS) in post-menopausal women with ER+/HER2- advanced breast cancer treated with the combination of Ibrance + letrozone compared to letrozole alone. Overall survival (OS) is was a secondary outcome. The median PFS was 20.2 months with combination treatment vs 10.2 months with letrozole alone (hazard ratio-0.488; 95% confidence interval, 0.319-0.748) and the median OS was 37.5 months on the combination compared to 33.3 months on letrozole alone (HR=0.813; 95% CI, 0.492-1.345, not a statistically significant difference).

Place in Therapy

Progression-free survival was significantly improved with the addition of palbociclib to letrozole during a randomized study in 165 patients, representing a chance for better quality of life for patients with metastatic breast cancer and later start of chemotherapy. While waiting on the phase III study results, in the absence of significant overall survival advantage at this time, the choice of treatment should be individualized, weighing in their potential benefit and side effect profile. The National Comprehensive Cancer Network (NCCN) guidelines have now included the combination of palbociclib + letrozole as a first-line endocrine therapy option for postmenopausal patients ER+/HER- metastatic breast cancer. The place in therapy will continue to evolve with upcoming trial results.

Comparative Pricing

Drug Regimen	Estimated Annual Cost
Ibrance + letrozole	$82,000
letrozole	$500
anastrazole	$465
exemestane	$485

Impact/Plan Management Suggestions

High impact. This new combination adding Ibrance to letrozole will significantly increase treatment costs in this patient population. Utilization should be managed to ensure that this combination is only used for patients who are likely to benefit.

Lunesta™ (eszopiclone)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02453207 – 1mg 02453215 – 2mg 02453223 – 3mg	Sunovion Pharmaceuticals Canada Inc.	28:24.92 – Miscellaneous Anxiolytics, Sedatives and Hypnotics

Indication(s)

Lunesta (eszopiclone) is indicated for the short-term treatment and symptomatic relief of insomnia including difficulty falling asleep, nocturnal awakenings or early morning awakenings.

Treatment with Lunesta should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for Lunesta should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

The use of hypnotics should be restricted for treating insomnia where disturbed sleep results in impaired daytime functioning.

Dose

The recommended starting dose is 1 mg. The dose can be increased to 2 mg or 3 mg if clinically indicated. Use the lowest effective dose of Lunesta possible for the patient. In some patients, the higher morning blood levels of Lunesta following use of the 2 mg or 3 mg doses increase the risk of next day impairment of driving and other activities that require full alertness. The dose of Lunesta should not exceed 3 mg, once daily immediately before bedtime.

Therapeutic Alternatives

Imovane (zopiclone)*; Sublinox (zolpidem)*

*generics available

Clinical Notes

Lunesta contains the active ingredient eszopiclone. Eszopiclone is a positive allosteric agonist at gamma-aminobutyric acid type A receptors (GABAA). Racemic zopiclone is a 1:1 mixture of the enantiomers (S)-zopiclone and (R)-zopiclone. Racemic zopiclone (also referred to as (RS)-zopiclone) is a short-acting hypnotic agent already marketed in Canada as Imovane and generics. It was recently added to the 18% generic price list by the pan-Canadian Pharmaceutical Alliance. Eszopiclone shares the sedative-hypnotic properties of zopiclone whereas the (R)-enantiomer has no hypnotic activity.

Eszopiclone has been touted to have a more rapid onset of action and a shorter duration of effect compared to (RS)-zopiclone which more effectively matches a conventional sleep cycle and should have a more desirable effect. This was based on pharmacokinetic studies rather than on clinical outcomes. When initially evaluated by the European Medicines Agency, it was not considered to be a New Active Substance since it was not judged to be demonstrably sufficiently different from (RS)-zopiclone, leading to a withdrawal of the application for marketing approval by the manufacturer in the EU.

Reviews and small head-to-head comparative trials versus zopiclone have shown that eszopiclone is comparable to zopiclone in terms of safety and effectiveness.

Place in Therapy

Lunesta is the third "z-drug" hypnotic to become available in Canada, the others being Imovane (zopiclone) and Sublinox (zolpidem). It may have more favourable pharmacokinetics compared to racemic zopiclone; however, the clinical benefits of this have not been demonstrated as meaningful differences in clinical outcomes.

Comparative Pricing

Drug	Estimated cost for one month
Lunesta	Price not available
zopiclone	$7-$14
zolpidem ODT	$36

Impact/Plan Management Suggestions

Insufficient information.

Lynparza™ (olaparib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Capsule	02454408 – 50mg	AstraZeneca Canada Inc.	10:00.00 – Antineoplastic Agents

Indication(s)

Lynparza (olaparib) is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. [NOC/c]

Platinum sensitivity is defined as disease progressing at least 6 months after completion of the penultimate platinum chemotherapy.

Dose

The recommended dose of Lynparza is 400 mg (eight 50 mg capsules) taken orally twice daily, equivalent to a total daily dose of 800 mg.

Therapeutic Alternatives

Avastin (bevacizumab) [in combination with platinum-doublet chemotherapy (e.g., carboplatin/gemcitabine) and/or as single agent after maximum chemotherapy treatment]

Clinical Notes

Ovarian cancer is the most fatal women's cancer in Canada. In 2015 it was estimated that approximately 2,800 Canadian women will be diagnosed with this disease and that ovarian cancer claims 1,750 lives in Canada. Because this disease is often caught in its late stages, 55% of women diagnosed die within five years. Based on 2010 estimates, about 1 in 71 Canadian women is expected to develop ovarian cancer during her lifetime and 1 in 91 will die from it. Only a small number of ovarian cancers (about 5%–10%) are related to a specific inherited genetic abnormality. Breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) normally help control the growth of cancer cells.

Lynparza is used for the 'maintenance' treatment of adult patients with high grade serous epithelial cancer of the ovary (a type of advanced cancer of the ovary), including cancer of the fallopian tubes (part of the female reproductive system that connect the ovaries to the uterus) and cancer of the peritoneum (the membrane lining the abdomen).

Lynparza is used in patients who have mutations in one of the two genes known as BRCA1 and BRCA2 and who have recurrent disease. Lynparza is given after treatment with platinum-based medicines, when the tumour is diminishing in size or has completely disappeared. It is given to those patients whose previous treatment with platinum-based medicines led to a durable response (lasting 6 months or more).

Lynparza, (olaparib) blocks the action of enzymes, called human poly (ADP ribose) polymerase (PARP), which help to repair damaged DNA in cells (both in normal and in cancer cells) during cell division. In normal cells there is an alternative mechanism for repairing DNA which requires BRCA1 and BRCA2 proteins. This alternative mechanism does not work properly in cancer cells with mutations in the BRCA1 or BRCA2 genes. Therefore, when PARP proteins are blocked, the damaged DNA in cancer cells cannot be repaired, and, as a result, the cancer cells die.

Lynparza has been shown to increase the time patients live without their disease getting worse in one main study involving 265 patients. Patients in the study had high grade serous ovarian cancers, including fallopian tube or peritoneal. Patients had undergone treatment with two or more regimens of platinum-based chemotherapy, and they had had a durable response (the cancer had not progressed for at least 6 months) before the last regimen. This response to platinum medicines justified the use of the last platinum-based treatment. Lynparza was given not later than 8 weeks after the last cycle of platinum-based medicines, when the tumour was diminishing in size or had completely disappeared. Around half of the patients in the study had BRCA mutations. These mutations were, in most cases, hereditary.

Patients who had a BRCA mutation and were treated with Lynparza lived on average significantly longer without their disease getting worse than patients who had a BRCA mutation and were treated with placebo: 11.2 months versus 4.3 months, respectively.

Place in Therapy

Lynparza is a chemotherapy sparing maintenance agent for treatment of platinum-sensitive BRCA-mutation positive women with ovarian cancer who are in response after retreatment for cancer recurrence. This can reduce the number of required cycles of chemotherapy to delay maximizing chemotherapy exposure and thereby prolong life.

Comparative Pricing

Drug	Estimated monthly or per cycle cost*	Estimated Annual Cost
Lynparza	$8,500	$102,000
Avastin*	$6,500	$112,000

* weight-based dosing assumes 70kg body weight

Impact/Plan Management Suggestions

Intermediate impact – high cost but cost-shift with low utilization.

Praluent™ (alirocumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02453819 – 75mg/ml (PFP) 02453835 – 150mg/ml (PFP) 02453754 – 75mg/ml (PFS) 02453762 – 150mg/ml (PFS)	Sanofi-Aventis Canada Inc.	24:06.24 – Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

PFP, Pre-filled pen; PFS, Pre-filled syringe

Indication(s)

Praluent is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

Dose

The recommended starting dose of Praluent is 75 mg administered subcutaneously once every 2 weeks. The majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Patients who require large reductions of LDL-C (>60%) or who have baseline LDL-C ≥8.33 mmol/L may be started directly on the 150mg dose.

Therapeutic Alternatives

Repatha (evolocumab)

Clinical Notes

Alirocumab is a fully human monoclonal antibody and acts as a lipid-lowering therapy which inhibits the enzyme PCSK9 (Proprotein Convertase Subtilisin/Kexin type 9). PCSK9 promotes degradation of the low-density lipoprotein receptor (LDLR), the primary receptor that clears atherogenic low-density lipoprotein cholesterol (LDL-C) from the circulation. By inhibiting PCSK9, alirocumab enhances recycling of the LDLR and leads to increased LDL-C clearance. Steady-state LDL-C is usually achieved after four weeks, which permits rapid dosage adjustment.

The primary endpoint in Phase III trials was percentage change in calculated LDL-C from baseline after 24 weeks – treatment with alirocumab resulted in a 46 to 61% reduction in LDL-C levels. Long-term Phase III studies are ongoing to evaluate the impact on major adverse CV events. One post-hoc analysis of data (LONG TERM trial) over a period of 78 weeks showed a statistically significant 48% lower rate of major CV events in the alirocumab group. The side effect profile for alirocumab was similar to placebo, making it a well-tolerated drug.

Place in Therapy

According to various Canadian studies, 31% to 36% of high CV-risk patients do not achieve LDL-C targets, despite the use of maximally tolerated statins with or without other lipid-lowering therapies. These patients are at higher risk for serious CV events. As for HeFH, its prevalence has been estimated to be at 1 in every 500 individuals. In the French Canadian population in Quebec, this is 1 in every 270, due to a founder effect.

Praluent is the second PCSK9 inhibitor available in Canada and has been found to be effective in reducing the level of serum LDL-cholesterol by 46 to 61%. Data is promising for reduction in cardiovascular endpoint occurrences; however, more solid data is expected soon.

Comparative Pricing

Drug	Estimated Annual Cost
Praluent	$7,700
Repatha	$7,700 (taken every 2 weeks)
	$11,000 (taken once a month)

Impact/Plan Management Suggestions

High impact – high cost drug; however, potential for cost shift from equally high cost therapy.

Praxbind™ (idarucizumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous injection	02454343 – 50mg/ml	Boehringer Ingelheim (Canada) Ltd.	92:12.00 - Antidotes

Indication(s)

Praxbind (idarucizumab) is an antidote, specific for dabigatran, and is indicated for adult patients treated with Pradaxa® when rapid specific reversal of the anticoagulant effects of dabigatran is required for:

- emergency surgery/urgent procedures
- life-threatening or uncontrolled bleeding

[NOC/c]

Dose

The complete dose of 5 g is administered intravenously, as two consecutive infusions over 5 to 10 minutes each, or as a bolus injection.

Therapeutic Alternatives

None

Clinical Notes

Praxbind is used to neutralise the effects of dabigatran (the active substance of Pradaxa), a medicine that treats and prevents blood clots. Praxbind is used to rapidly stop the anticlotting effect of dabigatran, before emergency surgery or in case of life-threatening bleeding. Praxbind (idarucizumab) is a monoclonal antibody fragment. Praxbind works by attaching firmly to dabigatran, and forming a complex in the blood. This rapidly stops dabigatran's anticlotting effect.

Praxbind has been investigated in three main studies involving 141 healthy adults who previously received dabigatran. In the studies, volunteers received either Praxbind or placebo after treatment with Pradaxa for 3.5 days. Results showed that Praxbind was able to completely neutralise Pradaxa's anticlotting effect within 5 minutes of use. In a still ongoing trial, an interim analysis showed similar results in 123 patients who had uncontrolled bleeding or required emergency surgery while using Pradaxa. Most patients in the study were taking Pradaxa to prevent stroke due to atrial fibrillation.

Place in Therapy

Praxbind is an antidote to Pradaxa (dabigatran) for patient who are experiencing severe bleeding or who require emergency surgery with serious bleeding risk. Due to this use, it is expected that the administration of this drug would be limited to the inpatient hospital setting.

Impact/Plan Management Suggestions

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

Ravicti™ (glycerol phenylbutyrate)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Oral liquid	02453304 – 1.1g/ml	Horizon Pharma Ireland Ltd.	40:10.00 – Ammonia Detoxicants

Indication(s)

Ravicti (glycerol phenylbutyrate) is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with Urea Cycle Disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti should be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).

Ravicti should be prescribed by a physician experienced in the management of UCDs.

Ravicti is not indicated for treatment of acute hyperammonemia in patients with UCDs.

Safety and efficacy for treatment of patients with N-acetylglutamate synthase (NAGS) deficiency have not been established.

Dose

The recommended total daily dose range of Ravicti is 4.5 mL/m2/day to 11.2 mL/m2/day (5.0 g/m2/day to 12.4 g/m2/day) and should take into account the following:

- The total daily dose should be divided into equal amounts and given with each meal or feeding (e.g. three times to six times per day).
- Each rounded up to the nearest 0.5 mL.

The recommended starting dosages for patients switching from sodium phenylbutyrate (Pheburane™) to Ravicti and patients naïve to phenylbutyric acid (PBA) may be different.

Patients switching from sodium phenylbutyrate to Ravicti should receive the dosage of Ravicti that contains the same amount of PBA. The conversion is as follows:

Total daily dosage of Ravicti (mL) = total daily dosage of sodium phenylbutyrate Tablets (g) x 0.86

Total daily dosage of Ravicti (mL) = total daily dosage of sodium phenylbutyrate Powder (g) x 0.81

Therapeutic Alternatives

Pheburane (sodium phenylbutyrate)

Clinical Notes

Ravicti is a medicine used long-term to manage urea-cycle disorders in adults and children from the age of two years, when the diseases cannot be managed by changes in their diet alone. Patients with urea cycle disorders are not able to get rid of waste nitrogen from the body because they lack some liver enzymes. In the body, waste nitrogen is turned into ammonia, which is harmful when it accumulates. Ravicti is used in patients who lack one or more of the following enzymes: carbamoyl phosphate synthetase-I, ornithine carbamoyltransferase, argininosuccinate synthetase, argininosuccinate lyase, arginase I and ornithine translocase.

Ravicti contains the active substance glycerol phenylbutyrate.

Because the number of patients with urea cycle disorders is low, the diseases are considered ‘rare diseases’.

The active substance in Ravicti, glycerol phenylbutyrate, is converted to phenylacetate in the body. Phenylacetate attaches to the amino acid glutamine found in proteins, which contains nitrogen, to form a substance that can be removed from the body by the kidneys.

This allows the levels of nitrogen in the body to decrease, reducing the amount of ammonia produced.

Ravicti has been compared with sodium phenylbutyrate (another medicine used to treat urea cycle disorders) in a study involving 88 adults with urea cycle disorders. The main measure of effectiveness was the change in the blood level of ammonia after 4 weeks of treatment. The study showed that Ravicti was at least as effective as the comparator in controlling the blood level of ammonia: the estimated average ammonia level was approximately 866 micromoles per litre in patients treated with Ravicti, compared with approximately 977 micromoles per litre in patients treated with sodium phenylbutyrate. Additional data from supportive studies showed a similar effect of Ravicti in children from 2 months of age.

UCDs are rare diseases. It is estimated that this affects between 500-600 Canadians.

Ravicti will be available in Canada under controlled distribution through Innomar Strategies.

Place in Therapy

Ravicti provides an alternative to Pheburane for the treatment of individuals with UCDs. Its availability in oral liquid form and at a higher phenylbutyrate concentration may allow for more convenient dosing.

Comparative Pricing

Drug	Estimated annual cost
Ravicti	$270,000
Pheburane	$140,000

Impact/Plan Management Suggestions

High impact – higher cost than alternative treatment, Pheburane

Sunvepra™ (asunaprevir)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Capsule	02452294 – 100mg	Bristol-Myers Squibb Canada	08:18.40 – HCV Antivirals

Indication(s)

Sunvepra (asunaprevir) 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 or 4 and compensated liver disease, including cirrhosis.

The following points should be considered when initiating treatment with Sunvepra:

- Treatment with Sunvepra should be initiated and monitored by a physician experienced in the treatment of CHC.
- Sunvepra must not be administered as monotherapy.
- Treatment regimen is dependent on viral genotype and subtype.
- Sunvepra has not been studied in patients who have previously failed therapy with a treatment regimen that includes asunaprevir or other HCV protease inhibitors.

Dose

The recommended dose of Sunvepra is 100mg twice daily for 24 weeks. The treatment regimen is dependent on viral genotype and subtype.

Therapeutic Alternatives and Comparative Pricing*

Sunvepra – unit cost: $42

*See table for alternate regimens and costs.

Patient Population	Regimen	Duration (weeks)	Cost
GT1a TN	**Sunvepra + Daklinza + PR[§] (QUAD)**	**24**	**$100,000-$180,000**
	Zepatier	12	$60,300
	Harvoni	12 (8)[a]	$71,000 ($47,000)
	Holkira Pak + RBV[b]	12	$59,000
	Sovaldi + Galexos[c]	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1b TN	**Sunvepra + Daklinza (DUAL)**	**24**	**$90,000-$170,000**
	Zepatier	12 (8)*	$60,300 ($40,200)*
	Harvoni	12 (8)[a]	$71,000 ($47,000)
	Holkira Pak	12	$59,000
	Sovaldi + Galexos	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]

(continued next page)

Patient Population	Regimen	Duration (weeks)	Cost
GT1a PR- or PI/PR-TE Relapsers	**Sunvepra + Daklinza + PR (QUAD)**	**24**	**$100,000-$180,000**
	Zepatier	12	$60,300
	Harvoni +/- RBV[f]	12-24[e]	$74,000-$141,000
	Holkira Pak + RBV[b]	12	$59,000
	Sovaldi + Galexos	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1b PR- or PI/PR-TE Relapsers	**Sunvepra + Daklinza (DUAL)**	**24**	**$90,000-$170,000**
	Zepatier	12	$60,300
	Harvoni +/- RBV[f]	12-24[e]	$74,000-$141,000
	Holkira Pak + RBV[b]	12	$59,000-$118,000
	Sovaldi + Galexos	12	$97,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1a PR- or PI/PR-TE on-treatment virologic failures	**Sunvepra + Daklinza + PR (QUAD)**	**24**	**$100,000-$180,000**
	Zepatier + RBV	16	$84,684-$85,541
	Harvoni +/- RBV[f]	12-24[e]	$74,000-$141,000
	Holkira Pak + RBV	24	$118,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT1b PR- or PI/PR-TE on-treatment virologic failures	**Sunvepra + Daklinza (DUAL)**	**24**	**$90,000-$170,000**
	Zepatier	12	$60,300
	Harvoni +/- RBV[f]	12-24[e]	$74,000-$141,000
	Holkira Pak +/- RBV[b]	12	$59,000
	Daklinza + Sovaldi	12-24[d]	$96,000 - $268,000[g]
GT4 TN or PR-TE Relapsers	**Sunvepra + Daklinza + PR[§] (QUAD)**	**24**	**$100,000-$180,000**
	Zepatier	12	$60,300
	Technivie + RBV[b]	12	$59,000
	Harvoni (off-label)	12	$71,000
	Sovaldi + RBV[f]	24	$123,000-$124,000

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Taltz™ (ixekizumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Subcutaneous injection	02455102 – 80mg/ml Auto-Injection 02455110 – 80mg/ml Syringe	Eli Lilly Canada Inc.	84:92.00 – Miscellaneous Skin and Mucous Membrane Agents

Indication(s)

Taltz (ixekizumab) is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Dose

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg (one injection) every 4 weeks.

Therapeutic Alternatives

Remicade, Humira, Enbrel, Cosentyx, Otezla, Stelara

Clinical Notes

Ixekizumab is an IgG4 monoclonal antibody that has a binding affinity of <3 pM to interleukin 17A (IL-17A), a naturally occurring proinflammatory cytokine. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines.

The safety and efficacy of Taltz were assessed in three multicentre, randomized, double-blind, placebo-controlled studies (UNCOVER-1, UNCOVER-2, and UNCOVER-3) in a total of 3866 patients 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, a static Physician Global Assessment (sPGA) score of ≥3 and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. The coprimary endpoints were the proportion of patients who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and the proportion of patients with an sPGA (0 or 1) (clear or minimal) with at least a 2-point improvement from baseline.

Efficacy Results at Week 12 in Adults with Plaque Psoriasis in UNCOVER-1, UNCOVER-2 and UNCOVER-3

	UNCOVER-1		UNCOVER-2		UNCOVER-3	
	TALTZ 80 mg Q2W (N=433) n (%)	Placebo (N=431) n (%)	TALTZ 80 mg Q2W (N=351) n (%)	Placebo (N=168) n (%)	TALTZ 80 mg Q2W (N=385) n (%)	Placebo (N=193) n (%)
sPGA of "0" (clear) or "1" (minimal)b	354 (82)	14 (3)	292 (83)	4 (2)	310 (81)	13 (7)
sPGA of "0" (clear)	160 (37)	0	147 (42)	1 (1)	155 (40)	0
PASI 75b	386 (89)	17 (4)	315 (90)	4 (2)	336 (87)	14 (7)
PASI 90	307 (71)	2 (1)	248 (71)	1 (1)	262 (68)	6 (3)
PASI 100	153 (35)	0	142 (40)	1 (1)	145 (38)	0

To evaluate the maintenance and durability of response, subjects originally randomized to Taltz and who were responders at Week 12 (i.e., sPGA of 0 or 1) in UNCOVER-1 and UNCOVER-2 were re-randomized to an additional 48 weeks of either a maintenance dose of Taltz 80 mg Q4W (every four weeks) or placebo. For responders at Week 12, the percentage of subjects who maintained this response (sPGA 0 or 1) at Week 60 (48 weeks following re-randomization) in the integrated trials (Trial 1 and Trial 2) was higher for subjects treated with Taltz 80 mg Q4W (75%) compared to those treated with placebo (7%). For responders at Week 12 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to relapse (sPGA ≥3) was 164 days in the integrated trials. Among these subjects, 66% regained a response of at least 0 or 1 on the sPGA within 12 weeks of restarting treatment with Taltz 80 mg Q4W

Place in Therapy

As another IL-17A inhibitor, Taltz is expected to occupy the same place in therapy as Cosentyx (secukinumab) as second- or third-line therapy after TNFα inhibitor failure as systemic therapy for plaque psoriasis.

Comparative Pricing

Drug	Estimated annual cost (maintenance)
Taltz	Price not available
Cosentyx	$23,000
Humira	$21,000
Remicade	$30,000
Otezla	$15,000

Impact/Plan Management Suggestions

Insufficient information.

Zontivity™ (vorapaxar)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02454815 – 2.5mg	Merck Canada Inc.	20:12.18 – Platelet Aggregation Inhibitors

Indication(s)

Zontivity (vorapaxar sulfate), co-administered with acetylsalicylic acid (ASA) with or without clopidogrel, according to their standard of care, is indicated for the reduction of atherothrombotic events in high-risk adult patients with a history of myocardial infarction (MI).

Dose

One tablet once daily.

Therapeutic Alternatives

Effient (prasugrel);
Brilinta (ticagrelor)

Clinical Notes

Patients with an established history of atherothrombotic or athero-ischemic disease are at particular risk of future cardiac or cerebral events, and vascular death.

Vorapaxar is a first-in-class selective antagonist of the protease-activated receptor 1 (PAR-1), the primary thrombin receptor on human platelets, which mediates the downstream effects of this critical coagulation factor in hemostasis and thrombosis. Thrombin-induced platelet activation has been implicated in a variety of cardiovascular disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention (PCI). As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet aggregation and thereby has the potential to reduce the risk of atherothrombotic complications of coronary disease.

In Canada, an estimated 1.6 million Canadians are living with heart disease or the effects of a stroke, 1.3 million are living with heart disease. More than 400,000 are living with long-term stroke disability. In 2012, more than 66,000 died from heart disease or stroke. (one person/7 minutes). In 2012, almost 14,000 Canadians died as the result of a heart attack. Each year more than 350,000 Canadians are hospitalized for heart disease or stroke. In 2011, more than 305,000 were hospitalized for heart disease. Recent incidence figures from the Chronic Disease and Injury Indicator Framework indicate that the incidence of ischemic heart disease in Canada is approximately 220,000 per year.

Place in Therapy

Zontivity is used as secondary prevention of cardiovascular events in individuals at high risk of a repeat event due to a history of a previous MI.

Comparative Pricing

Drug	Estimated Annual Cost
Zontivity	Price not available
Effient	$1,100
Brilinta	$1,200
Clopidogrel	$200

Impact/Plan Management Suggestions

Insufficient information.

FIRST TIME GENERICS

First Time Generic Drugs (Notices of Compliance (NOCs) from February 24, 2016 to June 08, 2016)

Generic Name	Reference Drug (Brand)	Rank by ingredient cost in 2015	Manufacturer	Route of Administration	Approved Indications/ Comments
Abacavir	Ziagen	819	Apotex Inc.	Oral	Nucleoside reverse transcriptase inhibitor (NRTI) for use in combination with other antiretroviral drugs for treatment of human immunodeficiency virus (HIV) infection.
Abacavir-Lamivudine	Kivexa	135	Apotex Inc.	Oral	NRTI combination used as part of a triple-drug regiment for treatment of HIV infection.
Paliperidone	Invega	614	Mylan Pharmaceuticals ULC	Oral	Schizophrenia and related psychotic disorders. Only 6mg strength approved.
Duloxetine	Cymbalta	9	several	Oral	Major depressive disorder (MDD); generalized anxiety disorder (GAD); diabetic peripheral neuropathy (DPN); chronic low back pain (CLBP); osteoarthritis (OA) of the knee
Escitalopram ODT	Cipralex Meltz	635	Actavis Pharma Company	Oral	Major depressive disorder (MDD); N.B., not approved for general anxiety disorder, obsessive compulsive disorder for which reference brand is indicated.
Anidulafungin	Eraxis	N/A	GenMed, a Division of Pfizer Canada Inc.	Intravenous injection	Invasive candidiasis/ candidemia in adult non-neutropenic patients

Health Newsflash

A Quarterly Publication

New Drugs and Pipeline News Reviewed at the April to June 2016 DEC Meetings

NEW DRUGS AND PRODUCT LINE EXTENSIONS

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from February 24, 2016 to June 8, 2016)

Band name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Truvada	emtricitabine/ tenofovir disoproxil fumarate	Gilead Sciences Canada, Inc.	Tablet	New indication	Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.
Natesto	testosterone	Acerus Pharmaceuticals Corporation	Nasal Gel	New dosage form	Intranasal gel indicated for use as testosterone replacement therapy.
S.O.S. Naloxone	naloxone	Sandoz Canada Incorporated	Intramuscular injection	New brand	New non-prescription brand indicated for emergency use outside of a hospital to reverse opioid overdose. Intended to be administered by a non-healthcare professional bystander.
Synflorix	pneumococcal 10-valent conjugate vaccine	GlaxoSmithKline Inc.	Intramuscular injection	New indication	Addition of Streptococcus pneumoniae cross-reactive serotype 19A to indication.
Entyvio	vedolizumab	Takeda Canada Inc.	Intravenous injection	New indication	Addition of Crohn's disease indication to ulcerative colitis.
Cosentyx	secukinumab	Novartis Pharmaceuticals Canada Inc.	Subcutaneous injection	New indication	Addition of psoriatic arthritis and ankylosing spondylitis to existing plaque psoriasis indication.
Xigduo	dapagliflozin/ metformin	AstraZeneca Canada Inc.	Tablet	New indication	Addition of use in combination with sulfonylurea and sitagliptin.
Keytruda	pembrolizumab	Merck Canada Inc.	Intravenous injection	New indication	Addition of use as first-line treatment for advanced melanoma and use in metastatic non-small cell lung cancer to existing second-line use in advanced melanoma.
Opdivo	nivolumab	Bristol-Myers-Squibb Canada	Intravenous injection	New indication	Addition of use as second-line treatment for advanced melanoma, use in metastatic non-small cell lung cancer and use in advanced or metastatic renal cell cardinoma to existing first-line use in advanced melanoma.
Descovy	emtricitabine/ tenofovir alafenamide	Gilead Sciences Canada Inc.	Tablet	New drug combination	Similar to existing fixed-dose combination drug Truvada, except that tenofovir disoproxil fumarate (TDF) is replaced by tenofovir alafenamide (TAF). TAF provides equivalent efficacy to TDF with potentially improved renal safety.

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EXPRESS SCRIPTS®

NEW DRUGS AND PRODUCT LINE EXTENSIONS (continued)

New Drugs and Product Line Extensions (Notices of Compliance (NOCs) from February 24, 2016 to June 8, 2016)

Band name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Esbriet	pirfenidone	Hoffmann La-Roche Limited	Capsule	New Indication	Treatment of idiopathic pulmonary fibrosis in adults (removal of mild to moderate severity specification)
BuTrans	buprenorphine	Purdue Pharma	Transdermal patch	New strength	15mcg/hour strength added
Metoject Subcutaneous	methotrexate	Medexus Inc.	Subcutaneous injection	New strengths and formulation	New formulation: subcutaneous injection (originally only intravenous and intramuscular injections)
Daklinza	daclatasvir	Bristol-Myers Squibb Canada	Tablet	New indication	Expansion of indication for hepatitis C virus infection with genotypes 1, 2, or 3 to include patients with: • HIV-1 co-infection • decompensated cirrhosis • HCV recurrence after liver transplantation
Invokamet	canagliflozin/ metformin	Janssen Inc.	Tablet	New drug combination	Fixed-dose combination of canagliflozin (Invokana) with metformin. Available in the following strengths: 50/500mg; 50/850mg; 50/1,000mg; 150/500mg; 150/850mg; 150/1,000mg.

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