Health Newsflash – A Quarterly Publication

New Drugs and Pipeline News Reviewed at the April to June 2013 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

Stivarga (regorafenib)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02403390 – 40mg	Bayer Inc.	10:00.00 – Antineoplastic agents

Indication(s)

Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

Dose

The recommended dose is 160 mg regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28day cycle. Treatment should be continued until disease progression or unacceptable toxicity.

Therapeutic Alternatives

None

Clinical Notes

Stivarga is a small molecule inhibitor of multiple membrane-bound and intracellular kinases (multi-kinase inhibitor) involved in a wide range of normal cellular functions and in pathologic processes, such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. The kinase inhibition profile of regorafenib affect the angiogenic (VEGFR 2/3, TIE2), stromal (PDGFR-ß, FGFR) and oncogenic (KIT, RET and B-RAF) cellular processes and pathways. This drug was approved for metastatic colorectal cancer based on one large phase III trial (The CORRECT trial) which showed that regorafenib is associated with statistically significant improvements in overall survival, progression-free survival, and disease control rate. Toxic effects included hand-foot syndrome and rash.

Place in Therapy

Stivarga, based on clinical trial data, has a role as fourth-line therapy for mCRC (after all other usual therapies have proven unsuccessful).

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Comparative Pricing

	Stivarga 40mg
Unit cost	$80
Cost per cycle (28 days)	$6,720
Cost for 3 cycles (median duration of treatment during phase 3 trial was 2.8 months)	$20,160

Impact/ Plan Management Suggestions

Intermediate impact. Manage using Prior Authorization to ensure appropriate utilization.

Neupro (rotigotine)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Transdermal patch	02403897 – 1mg 02403900 – 2mg 02403919 – 3mg 02403927 – 4mg 02403935 – 6mg 02403943 – 8mg	UCB Canada Inc	28:36.20 – Dopamine receptor agonists

Indication(s)

Canadian Product Monograph not available; information from FDA Prescribing Information
Neupro (Rotigotine Transdermal System) is indicated for the treatment of the signs and symptoms of idiopathic **Parkinson's disease** and for the treatment of moderate-to-severe primary **restless legs syndrome**.

Dose

Neupro patches are applied once daily. Dose ranges from 1-2mg/24 hours initially (depending on the indication) to a maximum of 3-8mg/24 hours.

Therapeutic Alternatives

bromocriptine*; Mirapex (pramipexole)*; ReQuip (ropinirole)* - all orally administered

*generics available

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Clinical Notes

Rotigotine is a non-ergot dopamine D2-agonist with similar actions to those of bromocriptine, but in contrast to bromocriptine (a dopamine D2-agonist) it also has agonist properties at D1 and D3 receptors. It is used as monotherapy in the management of Parkinson's disease, mainly in the early stage. It may also be used as an adjunct to levodopa therapy.

The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine receptors within the caudateputamen in the brain. The precise mechanism of action of rotigotine as a treatment for Restless Legs Syndrome is unknown but is thought to also be related to its ability to stimulate dopamine receptors.

Place in Therapy

Neupro can be used as monotherapy in early Parkinson's disease and in advanced Parkinson's disease with concomitant levodopa therapy. In advanced disease, Neupro may reduce the levodopa dose required to alleviate symptoms.
For moderate-severe primary restless legs syndrome, Neupro may reduce symptom severity.

Comparative Pricing

Price not available

Impact/Plan Management Suggestions

Insufficient information

Tecfidera (dimethyl fumarate)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Delayed release capsule	02404508 – 120mg	Biogen Idec Canada Inc.	28:92.00 - Miscellaneous Central Nervous System Agents

Indication(s)

Tecfidera (dimethyl fumarate) is indicated as monotherapy for the treatment of relapsing remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and to delay the progression of disability.

Dose

The initial dose is 120mg orally twice daily which should then be increased, after seven days, to the target maintenance dose of 240mg twice daily.

Therapeutic Alternatives

Oral therapy: fingolimod: Gilenya®;
Injectable therapies: glatiramer acetate: Copaxone®; interferon beta-1a: Avonex®, Rebif®; interferon beta-1b: Betaseron®, Extavia®; natalizumab: Tysabri®

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Clinical Notes

MS is a chronic neurologic disorder characterized by targeted destruction of central nervous system (CNS) myelin, as well as axonal degeneration and loss. The precise pathogenic mechanisms are not clearly understood, but in the early stages neural damage is thought to result from immune-mediated destruction of myelin. As a result of demyelination, the propagation of electrical nerve signals is interrupted, leading to a vast array of clinical symptoms including weakness, fatigue, cognitive difficulties, optic neuritis, bowel/bladder abnormalities and neuropathic pain. The areas of eroded myelin along CNS axonal tracts are referred to as lesions or plaques. Although there is no known cure for MS, several disease-modifying therapies have been shown to reduce the rate of relapses in RRMS, which may ultimately reduce/delay disease progression. The mechanism by which dimethyl fumarate (DMF) exerts its therapeutic effect in multiple sclerosis is unknown. DMF and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress.

Place in Therapy

Tecfidera (dimethyl fumarate) is an oral agent (the second one to become available) indicated for the treatment of adults with relapsing forms of multiple sclerosis. There is no data on its effectiveness in progressive forms of MS.

Pricing

	Tecfidera	Avonex	Copaxone	Gilenya
Unit cost	$17	$416	$47	$90
Annual cost	$24,300	$21,600	$17,150	$32,800

Impact/Plan Management Suggestions

Intermediate impact. Manage using Prior Authorization to ensure appropriate utilization.

Fycompa (perampanel)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Tablet	02404516 – 2mg 02404524 – 4mg 02404532 – 6mg 02404540 – 8mg 02404559 – 10mg 02404567 – 12mg	Eisai Limited	28:12.92 – Miscellaneous anticonvulsants

Indication(s)

Fycompa (perampanel) 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.

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Dose

The dose is individualized based on clinical response and tolerability. The recommended starting dose is 2 - 4mg once daily. The usual effective dose is 8 - 12mg once daily. Doses above the maximum 12mg/day have not been studied in patients.

Therapeutic Alternatives

Theoretically any other anti-epileptic drug but commonly used adjunctive agents include: clobazam*, gabapentin*, lacosamide (Vimpat®), oxcarbazepine*, phenobarbital*, primidone*, topiramate*, valproic acid/divalproex*, vigabatrin (Sabril®).
Fycompa has a unique mechanism of action.
* available as generic

Clinical Notes

Perampanel is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. However, the precise mechanism by which Fycompa exerts its antiepileptic effects in humans has not been fully elucidated. In three randomized, placebo-controlled, double-blind, multicenter trials, seizure frequency was statistically significantly reduced with perampanel doses of 4 mg/day, 8 mg/day, and 12 mg/day compared with placebo as adjunctive treatment of partial-onset seizures in adult and pediatric patients. The most common adverse effects reported with this drug include anxiety, confusion, imbalance, double vision, dizziness, gastrointestinal distress or nausea, imbalance and increased weight. The effects of Fycompa on tasks involving alertness and vigilance, such as driving, were additive to the effects of alcohol itself. Multiple doses of Fycompa increased levels of anger, confusion, and depression, particularly when taken with alcohol.

Place in Therapy

Fycompa is an anti-epileptic drug with has shown usefulness as adjunctive therapy for partial-onset seizures. Because of its unique mode of action, it may be effective in controlling seizures that have been resistant to other available treatments.

Comparative Pricing

	Fycompa	Vimpat	Sabril
Unit cost	$9.97 (flat)	$2.53 - $5.80	500mg: $0.96
Annual cost	$3,640	$1,847-$4,234	$1,400-$2,100

Impact/Plan Management Suggestions

Minimal impact – cost shift from similarly priced alternatives (i.e., other new-generation antiepileptic drugs).

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Perjeta (pertuzumab)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Intravenous Injection	02405016 – 420mg/14ml Vial [30mg/ml] Combo Pack (pertuzumab + trastuzumab): 02405024 – 420mg/vial + 440mg/vial	Hoffmann La Roche Limited	10:00.00 – Antineoplastic agents

Indication(s)

Perjeta™ (pertuzumab) is indicated in combination with Herceptin® (trastuzumab) and docetaxel for the treatment of patients with HER2- positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Dose

The recommended initial dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes. It is recommended that patients are treated with Perjeta until disease progression or unmanageable toxicity.

Therapeutic Alternatives

None

Clinical Notes

Pertuzumab is a recombinant humanized monoclonal antibody that specifically targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

Pertuzumab and trastuzumab bind to different sites (epitopes) on the extracellular receptor region of HER2 and show complementary mechanisms of action and together provide a more comprehensive blockade of HER2 and greater overall anti-tumour effect than either agent alone. Pertuzumab also blocks the dimerization of HER2 with other HER family members, thus inhibiting ligand-activated HER2 signaling.

Place in Therapy

Pertuzumab was specifically designed to bind to a different epitope on HER2 than trastuzumab. The distinct mechanisms by which pertuzumab and trastuzumab disrupt HER2 signaling result in augmented therapeutic efficacy when the two agents are administered in combination. Pertuzumab, while showing only limited activity as a single agent, resulted in slowed tumour growth or, even complete tumour regression when used in combination with trastuzumab.

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Comparative Pricing

	Perjeta	Perjeta-Herceptin Combo-Pack
Unit cost	$3,177	$5,877
Annual cost (17 cycles)	$54,009	$99,909

Impact/Plan Management Suggestions

Intermediate impact. Manage using Prior Authorization to ensure appropriate utilization.

Xtandi (enzalutamide)			
Dosage Form	**DIN & Strength**	**Manufacturer**	**AHFS Class**
Capsule	02407329 – 40mg	Astella Pharma Canada Inc.	10:00.00 – Antineoplastic agents

Indication(s)

Xtandi (enzalutamide capsules) is indicated for the treatment of patients with metastatic castration-resistant prostate cancer in the setting of medical or surgical castration in patients who have received docetaxel therapy.

Dose

The recommended dose is 160 mg (four 40 mg capsules) as a single oral daily dose.

Therapeutic Alternatives

Jevtana (cabazitaxel); Zytiga (abiraterone acetate)

Clinical Notes

Enzalutamide, an androgen receptor inhibitor, competitively inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA. The major active metabolite, N-desmethyl enzalutamide, has similar activity. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro and decreased tumor volume in an animal study.

Xtandi is for use in patients who are maintaining treatment with a GnRH analogue or who have had previously undergone surgical castration. Patients started on Xtandi who are receiving a GnRH analogue should continue to receive a GnRH analogue.

Most significant serious adverse effect is seizure which is dose related. Other common adverse effects include fatigue (33.6%), hot flush (20.3%) and headache (11.6%).

As opposed to abiraterone and cabazitaxel, adjunctive steroid therapy (e.g., prednisone) is not required.

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Place in Therapy

Enzalutamide is indicated to treat metastatic castration-resistant prostate cancer in men who have previously received docetaxel. Enzalutamide significantly improved overall survival (OS) (18.4 vs 13.6 months), FACT-P quality-of-life response (43% vs 18%), PSA response rate (54% vs 2%), and soft-tissue response rate (29% vs 4%) compared with placebo in an international, phase 3, randomized, double-blind, trial (n=1199) of men with metastatic castration-resistant prostate cancer after chemotherapy that included docetaxel. OS is similar to Zytiga, slightly better than Jevtana.

Pricing

	Xtandi	Zytiga
Unit cost	$30	$30
Monthly cost	$3,600	$3.600

Impact/Plan Management Suggestions

Minimal impact – cost shift from a similarly priced therapeutic alternative with similar efficacy. Manage using Prior Authorization to ensure appropriate utilization.

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FIRST TIME GENERICS

First-Time Generic Drugs (Notices of Compliance from Mar 6, 2013 to May 29, 2013)

Generic Name	Reference Drug (Brand)	Rank by ingredient cost in 2012	Manufacturer	Route of Administration	Approved Indications
quetiapine XR	Seroquel XR	42	Teva Canada Limited	Oral	Schizophrenia, bipolar disorder, major depressive disorder
mometasone nasal spray	Nasonex	29	Apotex Incorporated	Intranasal	Allergic rhinitis, rhinosinusitis (adjunctive), nasal polyps
alendronate/ cholecalciferol	Fosavance	316	Teva Canada Limited	Oral	Osteoporosis
imatinib	Gleevec	57	Teva Canada Limited	Oral	Leukemia
ganciclovir for Injection	Cytovene	1069	Pharmaceutical Partners of Canada Inc	Intravenous	Cytomegalovirus
eptafibatide Injection	Integrilin	-	Teva Canada Limited	Intravenous	Acute Coronary Syndrome
cistracurium besylate Injection	Nimbex	-	Agila Specialties	Intravenous	Skeletal muscle relaxant for adjunctive use in general anesthesia
Tricira Lo	Tri-Cyclen Lo	46	Apotex Incorporated	Oral	Contraceptive, Acne
fondaparinux sodium Injection	Arixtra	860	Dr. Reddys Laboratories Ltd.	Intravenous/ Subcutaneous	Anticoagulant

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PRODUCT LINE-EXTENSIONS

Product Line-Extension (Notices of Compliance from Mar 6, 2013 to May 29, 2013)

Brand name	Chemical name	Manufacturer	Dosage form	Type of Line Extension	Specifics/Comments
Jentadueto	linagliptin/ metformin	Boehringer Ingelheim Canada Ltd.	Tablet	New drug combination	Fixed-dose combination of metformin and DPP-4 inhibitor, linagliptin (Trajenta)
Estrogel ProPak	estradiol gel/ progesterone capsules	Merck Canada Inc	Transdermal gel/ Capsule	New drug combination	Combination in same package of Estragel (estradiol gel) and Prometrium (progesterone) capsules
Xerese	acyclovir/ hydrocortisone	Valeant Canada LP	Cream	New drug combination	Combination of topical antiviral acyclovir with hydrocortisone intended to speed healing of recurrent herpes labialis lesions
Omnaris HFA	ciclesonide	Takeda Canada Inc	Metered-dose nasal aerosol	New formulation	New formulation of existing product
Xarelto	rivaroxaban	Bayer Inc	Tablet	New indication	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE
Uvadex	methoxsalen	Therakos Inc	Extracorporeal solution	New brand	For extracorporeal treatment of white blood cells prior to photophoresis
Alimta	pemetrexed	Eli Lilly Canada Inc.	Intravenous injection	New indication	Extension of maintenance therapy in Nonsquamous Non-Small Cell Lung Cancer following initial chemotherapy
Abilify	aripiprazole	Bristol-Myers Squibb Canada	Tablet	New indication	Adjunctive treatment of Major Depressive Disorder

Authors: Aaron Aoki, RPh, BScPhm, MBA, CDE | Priscilla Po, PharmD, RPh

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