Product Update

ADVISORIES

AstraZeneca Canada Inc. in consultation with Health Canada informs health care professionals of QTc prolongations, torsade de pointes and sudden death associated with **Caprelsa** (vandetanib), based on reports of these events in clinical trials. Caprelsa is available through a Restricted Distribution Program and may only be prescribed by physicians who have completed mandatory online training. A risk and benefit analysis should be carefully conducted prior to Caprelsa initiation.

Health Canada is advising Canadians that Vita Health Products is conducting a voluntary recall of 5 lots of **Compliments Extra Strength Acetaminophen Gelcaps** 500 mg (bottles of 120 gelcaps). The product is being recalled because its packaging suggests it is child-resistant, but it has been packaged with a non-child-resistant cap.

In collaboration with Health Canada, the manufacturers of **domperidone** inform health care professionals of the association of domperidone maleate with serious ventricular arrhythmias and sudden cardiac death, especially in patients taking daily doses >30 mg and in patients >60 years of age. The association is based on the results of a population-based case-control study conducted in the Netherlands. The adjusted odds ratio for sudden cardiac death with daily doses >30 mg was 11.4 (95% CI 1.99, 65.2). An increased risk of a composite endpoint of sudden cardiac death and serious ventricular arrhythmia was observed in patients >60 years with oral domperidone, according to the results of a nested case-control study using the administrative databases of Saskatchewan Health

(adjusted OR 1.64; 95% CI 1.31, 2.05). Limit administration of domperidone to the lowest possible dose. Titrate the dose with caution while weighing the benefits with the potential risks. Monitor for drug-drug interactions that can elevate domperidone levels. The coadministration of ketoconazole with domperidone is contraindicated.

Janssen Inc. and Health Canada inform health care professionals of new safety information regarding the use of **Doribax** (doripenem for injection) in the treatment of ventilator-associated pneumonia (VAP). According to the results of a prospective, randomized, double-blind, double-dummy multicenter Phase III trial in patients with VAP, a higher mortality rate and a lower clinical cure rate were seen in those using Doribax 1 g (4-hour infusion) every 8 hours in a fixed 7-day course compared to those using imipenem-cilastatin 1 g (1-hour infusion) every 8 hours in a fixed 10-day course. The product monograph for Doribax will be updated with this information.

Health Canada concludes that long-term daily use (over 4 years) of **finasteride** 5 mg (Proscar, Propecia) and **dutasteride** (Avodart, Jalyn) in men ≥ 50 years is associated with a small but statistically significant increased risk of high-grade prostate cancer and the benefits of preventing low-grade prostate cancer are small relative to the risk of developing high-grade prostate cancer. The conclusion is based on the results of 2 large international clinical trials: the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events. Finasteride is also available in 1 mg tablets; this strength was not included in the review, however, the potential risk

of high-grade prostate cancer with this strength has not been ruled out. Finasteride and dutasteride are not approved for the prevention of prostate cancer in Canada. The monographs for the brand name products have been updated to reflect these messages; the product monographs for generics will follow.

In consultation with Health Canada, the manufacturers of **fluoroquinolone antibiotics** (Bayer and Janssen Inc.) inform health care professionals of the association of these antibiotics (Avelox, Cipro, Cipro XL, Levaquin) with worsening symptoms of myasthenia gravis. Based on a review of postmarketing reports of serious adverse events, deaths and the requirement of ventilator support have been associated with fluoroquinolone use patients with myasthenia gravis. Fluoroquinolone antibiotics should be avoided in patients with a known history of myasthenia gravis, as these antibiotics have neuromuscular blocking activity. The Warnings and Precautions section of the product monographs have been updated to reflect this information.

A safety review of **Gilenya** is being conducted by Health Canada due to reports of serious adverse events. Though there have been no deaths reported in Canada, 11 deaths have been reported internationally. Three deaths involved heart attacks, 1 involved a disturbance of the heart rhythm and 7 reports are unexplained, including 1 report in the US involving a patient who died within 24 hours of taking the first dose. Currently, it is unclear whether these deaths were caused by Gilenya or other factors. Health Canada emphasizes the recommendations stated in the product monograph, particularly with respect to patient monitoring.

ADVISORIES (cont'd)

Other physician recommendations include obtaining an ECG before the first dose if an ECG from the last 6 months is not available, observing patients for signs and symptoms of slow heart rate, including a periodic assessment of heart rate for at least 6 hours after the first dose or if more than 2 weeks have passed since the previous dose, initiating appropriate treatment if heart-related symptoms occur and measuring blood pressure regularly, as Gilenya is known to increase blood pressure.

Sandoz Canada has initiated a voluntary recall of a portion of one lot of 2 mg/mL (1 mL) **Morphine Sulfate Injection** (Lot #CC2824 exp. 12/2014, DIN 02242484, UPC 057513056420) from the Canadian market. This recall was prompted after a Toronto hospital reported that a box labelled as morphine ampoules incorrectly contained isoproterenol ampoules. At the time, the remaining undistributed inventory was being inspected to confirm that all the packages contained the correct product prior to release to the market. Recalled products will not be released. Consumers can contact Sandoz Canada directly at 1-877-650-0751 for more information about the recall or how to return the affected product.

Due to postmarketing reports of serious bleeding with the use of **Pradax**, the product monograph has been updated with new recommendations regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves. As renal impairment is a risk factor for bleeding with Pradax, renal function should be assessed in all patients prior to initiation of treatment. Pradax is not recommended in patients with CrCl <30 mL/min. In patients who are >75 years or in those whose CrCl is 30–50 mL/min, renal function should be assessed at least once a year. Routine measuring of renal function is also rec-

ommended for patients in situations where a rapid decline in renal function is anticipated. Due to a lack of safety and efficacy data, Pradax is not recommended in patients with hemodynamically significant rheumatic valvular heart disease, especially mitral stenosis, or in patients with prosthetic heart valves.

Health Canada informs health care professionals of a possible association between **proton pump inhibitors** (PPIs) and an increased risk of *Clostridium difficile*-associated diarrhea (CDAD). The risk of infection is increased in patients with advanced age, severe underlying illness, hospitalization or antibiotic use. Although a definite association has not been confirmed, the possibility has not been ruled out, as there have been a number of studies suggesting a possible link between PPIs and increased risk of CDAD. Advise patients to seek attention immediately if they are taking a PPI and develop diarrhea that does not improve.

Vita Health Products is conducting a voluntary recall of lot #00058398B of the “combo pack” **Rexall Extra Strength Sinus Relief Daytime and Nighttime Caplets** due to a labelling error, where the text printed on the blister foil incorrectly identifies the nighttime caplets as the daytime caplets and vice versa. A nighttime caplet taken during the day may result in drowsiness and negative consequences for patients engaging in activities requiring alertness, such as driving. Consumers can contact Vita Health Products at 1-800-665-8820 for more information about the recall.

Janssen Inc. and Health Canada inform health professionals of fatal outcomes associated with inadvertent intrathecal administration of **Velcade**

(bortezomib). Three cases of fatal outcomes have occurred in France and Italy; there have been no reports in Canada. Because these cases occurred when intrathecal chemotherapy and Velcade intravenous administration were scheduled simultaneously, Janssen Inc. encourages health care professionals to administer these therapies at different times. Further, the company suggests labelling the syringes clearly with the name of the medication and the appropriate route of administration, while ensuring that the labelling is double-checked prior to administration to reduce the risk of error.

NEW PRODUCTS

Asmanex Twisthaler (mometasone furoate 200 mcg and 400 mcg/metered inhalation in a dry powder inhaler by Merck Canada Inc.) is an orally inhaled corticosteroid (ICS) indicated for the prophylactic management of steroid-responsive bronchial asthma in patients ≥ 12 years. Asmanex Twisthaler is not indicated for the relief of acute bronchospasm. It has a similar adverse effect profile to that of other orally inhaled ICS. Usual recommended daily dose is 400 mcg by oral inhalation once daily in the morning. Patients on previous high doses of inhaled corticosteroids may be more adequately controlled on 400 mcg daily, given in 2 divided doses (200 mcg twice daily). A dose of 400 mcg used once daily or a dose reduction to 200 mcg once daily may be an effective maintenance dose for some patients. For patients with severe asthma who require oral corticosteroids, the recommended starting dose is 400 mcg twice daily; this is the maximum recommended dose

that can be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. Systemic cortico-

NEW PRODUCTS (cont'd)

steroids should be slowly tapered and patients observed for signs and symptoms of adrenal insufficiency. Asmanex Twisthaler can then be tapered to the minimum maintenance dose. Advise patients not to abruptly stop treatment with Asmanex Twisthaler; it is recommended to taper the dose gradually. Advise patients to hold the device vertically to load prior to use. The device comes with a dose counter. Gargle and rinse mouth with water and spit water out after each dose to prevent *Candida albicans* infection of the mouth and pharynx.

Arzerra (ofatumumab 100 mg/5 mL or 1000 mg/50 mL vials by GlaxoSmith-Kline Inc.) is an IgG1 κ human monoclonal antibody that has received an NOC/c for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. Efficacy of Arzerra is based on the demonstration of durable objective responses. There are no data to demonstrate an improvement in the disease-related symptoms or increased survival. Contraindications include patients who have or have had progressive multifocal leukoencephalopathy. Arzerra is administered as an intravenous infusion and must be diluted prior to administration; it is not to be administered as an intravenous push or bolus. Arzerra is administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available. It is administered with in-line filter supplied with product.

Premedication with oral acetaminophen 1000 mg or equivalent, oral or intravenous antihistamine (cetirizine 10 mg or equivalent) and intravenous corticosteroid (prednisolone 100 mg or equivalent) is recommended 30 minutes to 2 hours prior to each dose. Please consult

the product monograph for more information.

Eliquis (apixaban 2.5 mg tablets by Pfizer Canada Inc.) is a direct factor Xa inhibitor indicated for the prevention of venous thromboembolic events in adult patients who have undergone elective knee or hip replacement surgery. Oral Eliquis works as well as enoxaparin to prevent thrombosis after surgery, with a similar bleeding risk. Contraindications include clinically significant active bleeding, lesions at increased risk of clinically significant bleeding such as cerebral infarct in the previous 6 months, hepatic disease associated with coagulopathy and clinically relevant bleeding risk and concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-glycoprotein. The recommended dose is 2.5 mg orally twice daily taken with or without food starting 12 to 24 hours after surgery. No dose adjustment is recommended in patients with CrCl ≥ 30 mL/min. Use Eliquis with caution in patients with CrCl 15–29 mL/min due to limited clinical experience and because these patients are at a higher risk of bleeding. Eliquis is not recommended for patients with CrCl < 15 mL/min or for patients on dialysis. The recommended duration

of treatment is 32 to 38 days in patients undergoing hip replacement surgery and 10 to 14 days in patients undergoing knee replacement surgery.

Halaven (eribulin mesylate injection 0.5 mg/mL by Eisai Limited) is a non-taxane microtubule dynamics inhibitor indicated for the treatment of patients with metastatic breast cancer who

have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane administered in either the adjuvant or metastatic setting. Hypokalemia, hypocalcemia and hypomagnesemia

should be corrected prior to initiation of therapy. ECG monitoring is recommended in patients with risk factors for torsade de pointes, such as patients with cardiac disease and patients on concomitant medications that prolong the QT interval. The recommended dose is 1.4 mg/m² administered IV over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle initiated in patients with ANC values ≥ 1500 cells/mm³ and platelets $> 100,000$ /mm³. Patients should be assessed for peripheral neuropathy and complete blood counts should be obtained prior to each dose. Halaven should not be diluted or administered through an IV line containing solutions with dextrose. Consult the product monograph for further information on recommended dose delays and dose reductions.

Lodalis (colesevelam 625 mg tablets by Valeant Canada LP) is a bile acid sequestrant indicated for the reduction of cholesterol blood levels in patients with hypercholesterolemia (Frederickson Type IIa). It is to be used as an adjunct to diet and lifestyle changes, when the response to these measures has been inadequate in patients who are not adequately controlled with an HMG-CoA reductase inhibitor alone or who are unable to tolerate a statin. Contraindications include bowel or biliary obstruction. Lodalis may affect the bioavailability of medications given concomitantly. Advise patients to take medications such as phenytoin and levothyroxine 4 hours prior to taking Lodalis. Patients who are taking warfarin may require more frequent INR monitoring upon initiation of Lodalis and then periodically thereafter. Lodalis is taken with meals and liquid. As monotherapy, the recommended starting dose is 3 tablets twice daily or 6 tablets once daily. The maximum recommended daily dose is 7 tablets. If used in combination, the recommended dose of Lodalis is 4 to 6 tablets per day. Advise patients to continue with the cholesterol-lowering diet.

NEW PRODUCTS (cont'd)

Luxiq (betamethasone valerate 0.12% foam by GlaxoSmithKline Inc.) is a topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestation of moderate to severe psoriasis of the scalp for up to 4 weeks of therapy in adult patients (≥ 18 years). Advise patients to apply a thin layer to the affected area(s) twice daily, in the morning and the evening, for a maximum of 4 weeks. An emollient should be continued as maintenance therapy. Advise patients to avoid abrupt discontinuation once control is achieved, as rebound of pre-existing dermatoses can occur. If no improvement is seen within 2 weeks, advise patients to visit their primary practitioner. Patients should dispense a small amount on a clear saucer or other, clean surface and not dispense directly on hands as the foam will be going to melt immediately upon contact with warm skin. Gently massage foam into affected area until foam disappears. Use sparingly. Allow the areas to dry naturally. Avoid fire, flame or smoking during and immediately following application, as the propellant in Luxiq foam is flammable.

Oleptro (trazodone hydrochloride 150 mg and 300 mg extended-release caplets by Angelini Labopharm LLC) is indicated for the symptomatic relief of major depressive disorder. Oleptro may be better tolerated than immediate-release trazodone due to blood levels being lower and more constant. The recommended starting dose is 150 mg once daily, taken in the late evening on an empty stomach, as high-fat meals can significantly increase its absorption. The dose may be increased by 75 mg daily every 3 days; the maximum daily dose is 375 mg. Advise patients that the tablets are scored and can be halved; however, chewing or crushing the tablet will destroy the slow-release mechanism.

nism. Common side effects include somnolence, sedation, fatigue and blurred vision. Priapism has been reported in postmarketing adverse drug reactions.

Onbrez Breezhaler (indacaterol maleate inhalation powder hard capsules 75 mcg by Novartis Pharmaceuticals Canada Inc.) is the first long-acting beta²-agonist (LABA) indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with (COPD), including chronic bronchitis and emphysema; other LABAs are used twice daily. Onbrez Breezhaler has a similar adverse effect profile to that of other inhaled LABAs currently on the market. Onbrez Breezhaler is not indicated for the relief of acute deterioration of COPD or for asthma use. The recommended dose is the once-daily oral inhalation of the contents of one 75 mcg capsule using the Breezhaler inhaler. Long-term benefit is unknown as there is no data for usage beyond 52 weeks.

OxyNEO (oxycodone hydrochloride controlled-release tablets by Purdue Pharma) is a long-acting oxycodone indicated for the relief of moderate to severe pain requiring the continuous use of an opioid analgesic preparation for several days or more. OxyNEO replaces OxyContin, which is being phased out this year. To help reduce risk of abuse of OxyNEO, the tablets have been hardened by a unique process to reduce the risk of being broken, crushed or chewed. Because of its hydrogelling properties, advise patients not to pre-soak, lick or wet OxyNEO prior to placing in the mouth. The medication should be taken with enough water to ensure complete swallowing immediately after placing it in the mouth, as

there have been postmarketing reports of choking, gagging, regurgitation and tablets stuck in the throat. If multiple tablets are prescribed, advise patients to swallow 1 tablet at a time. Patients who have difficulty swallowing or who have been diagnosed with narrowing of the esophagus should not use OxyNEO. Avoid administering OxyNEO via nasogastric, gastric or other feeding tubes, as it may cause obstruction of feeding tubes. Please consult product monograph for dosing recommendations.

Rapaflo (silodosin 4 mg and 8 mg immediate-release capsules by Watson Laboratories, Inc.) is a selective alpha-blocker indicated for the treatment of benign prostatic hyperplasia (BPH). Rapaflo is contraindicated in patients with CrCl < 30 mL/min and those with severe hepatic impairment (Child-Pugh score ≥ 10). Common adverse effects include retrograde ejaculation (reversible upon discontinuation of Rapaflo) and dizziness. The recommended daily dose is 8 mg once daily with a meal; the dose is 4 mg once daily in patients with CrCl 30–50 mL/min. The capsules can be opened and the powder sprinkled on a spoonful of applesauce and swallowed immediately without chewing, followed with a glass of cool water to ensure complete swallowing of the powder.

Resotran (prucalopride 1 mg and 2 mg tablets by Janssen Inc.) is a selective, high-affinity serotonin (5-HT₄) receptor agonist indicated for the treatment of

NEW PRODUCTS (cont'd)

chronic idiopathic constipation in adult female patients in whom laxatives failed to provide adequate relief. Consider alternate therapy if treatment with prucalopride is not effective during the first 4 weeks. Efficacy has not been established beyond 3 months of duration. Common dose-related adverse effects include nausea, abdominal pain, diarrhea and headache. The recommended daily dose is 2 mg once daily for adults 18 to 65 years. Advise patients to inform their doctor if there is no bowel movement in 3–4 days as an add-on laxative should be considered. For patients >65 years, the recommended daily dose is 1 mg once daily, titrated to 2 mg once daily if warranted. For patients with GFR <30 mL/min, the recommended daily dose is 1 mg once daily.

Somatuline Autogel (lanreotide 60 mg, 90 mg and 120 mg/syringes by Ipsen Biopharm Limited) is a synthetic octapeptide analogue of natural somatostatin. It is indicated for the long-term treatment of patients with acromegaly due to pituitary tumors who have had inadequate response to or cannot be treated with surgery and/or radiotherapy and for the relief of symptoms associated with acromegaly. Contraindications include complicated, untreated lithiasis of the bile ducts. Initial dose is 90 mg administered via deep subcutaneous route at 4-week intervals for 3 months, in the superior external quadrant of the buttock, or in cases of self-administration, patients can inject in the upper outer thigh, alternating between the left and right sides. Refer to the product monograph for further information regarding how the dose may be adapted after 3 months of use.

NEW INDICATIONS

Abilify (aripiprazole by Bristol Myers Squibb Canada) is now approved for the acute treatment of manic or mixed epi-

sodes in bipolar 1 disorder as monotherapy in adolescent patients 13–17 years of age.

Afinitor (everolimus by Novartis Pharmaceuticals Canada Inc.) is now approved for the treatment of progressive neuroendocrine tumours of pancreatic origin in patients with unresectable, locally advanced or metastatic disease.

NEW ROUTE

Velcade (bortezomib mannitol boronic ester by Janssen Inc.) is now approved for subcutaneous administration (at a concentration of 2.5 mg/mL) in addition to intravenous bolus injection (at a concentration of 1 mg/mL). Use caution when calculating the volume to be administered, as each route of administration has a different reconstituted concentration.

NEW GENERICS

Esomeprazole 20 mg tablets are now available from Apotex Inc. This is a new alternative to Nexium.

Finasteride 5 mg tablets are now available from Apotex Inc. This is a new alternative to Proscar.

Levofloxacin 500 mg tablets are now available from Apotex Inc. This is a new alternative to Levaquin. 250 mg and 750 mg tablets are also available.

Mycophenolate 500 mg tablets are now available from Cobalt Inc. This is a new alternative to CellCept.

Risedronate 35 mg tablets are now available from Mylan Inc. This is a new alternative to Actonel.

Rizatriptan 5 mg and 10 mg ODT are now available from Cobalt Inc and Sandoz Canada. This is a new alternative to Maxalt RPD.

Rosuvastatin 5 mg, 10 mg, 20 mg and 40

mg tablets are now available from Apotex Inc., Teva Canada and Sandoz Canada. This is a new alternative to Crestor.

DISCONTINUED PRODUCTS

CoActifed (tripolidine hydrochloride, codeine phosphate, pseudoephedrine hydrochloride) syrup pack size of 2 L has now been discontinued. The 100 mL pack size continues to be available.

Fraxiparine (nadroparin calcium 7600 anti-Xa IU/mL) by GlaxoSmithKline Inc. has been discontinued. Fraxiparine 9500 anti-Xa IU/mL and Fraxiparine Forte 19,000 anti-Xa IU/mL continue to be available.

Rythmodan (disopyramide) 100 mg capsules by Sanofi-Aventis Canada Inc. have now been discontinued. The 150 mg capsules continue to be available.

NEW COMBINATION PRODUCTS

Complera capsule-shaped, film-coated tablets by Gilead Sciences contain a combination of emtricitabine 200 mg, rilpivirine 25 mg and tenofovir disoproxil fumarate 300 mg. ■

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