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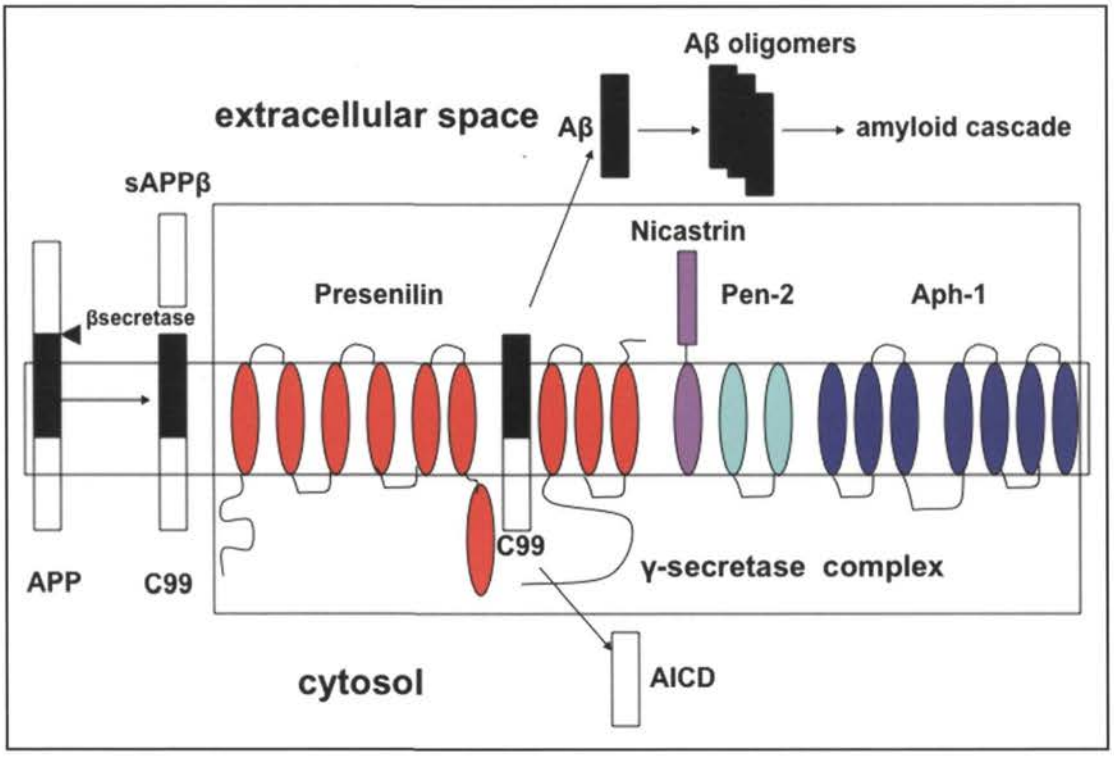


**Early-Onset Familial Alzheimer's Disease (EOFAD)**

*Liyong Wu, Pedro Rosa-Neto, Ging-Yuek R. Hsiung, A. Dessa Sadovnick, Mario Masellis, Sandra E. Black, Jianping Jia, Serge Gauthier*

***Review Article - Can J Neurol Sci. 2012; 39: 436-445***

*Schematic illustration of amyloidogenic proteolytic pathway. The amyloidogenic pathway starts with β-secretase cleavage of APP, yielding sAPPβ and C99. C99 follows further γ-secretase complex proteolysis yielding AICD in cytosol and soluble Aβ peptide (predominately Aβ42 and Aβ40) in the extracellular space. The γ-secretase complex comprises of preseninlin, nicastrin, pen-2 and aph-1. Cleavage of C99 occurs in the active site of preseninlin. Aβ monomers subsequently aggregate in the extracellular space to form soluble oligomers, and eventually deposit into insoluble amyloid plaques, starting a cascade of down-stream pathological processes. Abbreviation: APP—amyloid precursor protein, sAPPβ—soluble amyloid precursor protein β production, AICD—amyloid intracellular domain, C99—C-terminal fragment of 99 amino acids in the membrane.*

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## EDITORIALS



## REVIEW ARTICLES



## ORIGINAL ARTICLES

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## NEUROIMAGING HIGHLIGHT



## BRIEF COMMUNICATIONS



## MEMORIAM



## LETTERS TO THE EDITOR



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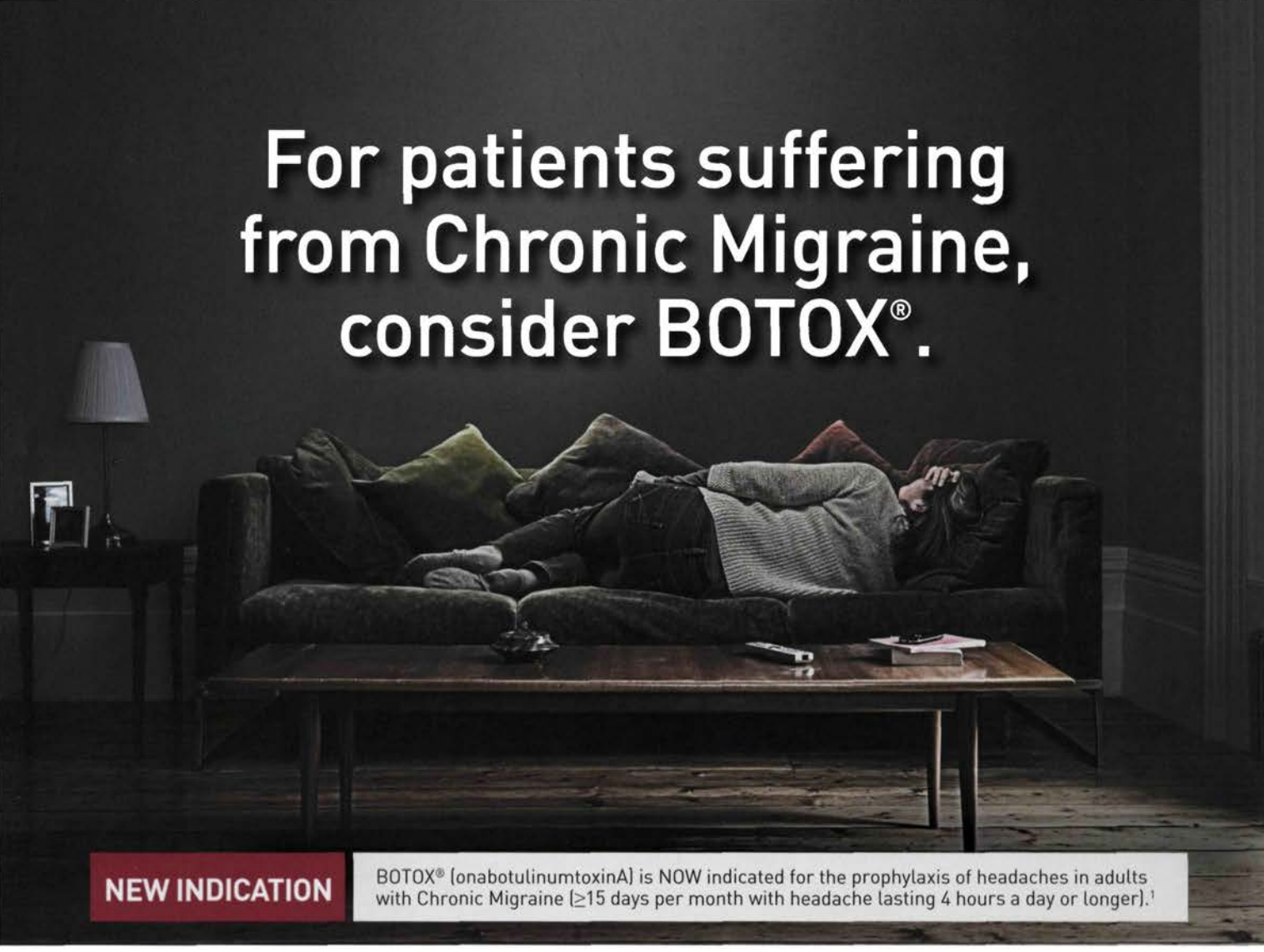


## For more information visit www.BOTOX.ca and enter the password CMBOTOX

BOTOX® is contraindicated in: patients who are hypersensitive to botulinum toxin type A or to any ingredient in the formulation or component of the container; the presence of infection at the proposed injection site(s).[1]

**The term "Allergan unit" upon which dosing is based is a specific measurement of toxin activity that is unique to Allergan's formulation of botulinum toxin type A. Therefore, the "Allergan units" used to describe BOTOX® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX® activity are not interchangeable with other products.[1]**

The safety and effectiveness of BOTOX® in the prophylaxis of headaches in Chronic Migraine has not been investigated in children and adolescents under 18 years of age or adults over 65 years of age.[1]

No efficacy has been shown for BOTOX® in the prophylaxis of headaches in patients with Episodic Migraine (<15 headaches days per month).[1]

BOTOX® for Chronic Migraine has not been evaluated in clinical trials beyond 5 injection cycles.[1]

BOTOX® should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment. Follow the recommended dosage and frequency of administration for BOTOX®.[1]

Caution should be used when BOTOX® is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle.[1]

Muscle weakness remote to the site of injection and other serious adverse effects (e.g. dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, in some cases associated with a fatal outcome.[1]

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.[1]

As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.[1]

There have been rare reports following administration of botulinum toxin of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. The exact relationship of these events to BOTOX®/BOTOX COSMETIC® is unknown.[1]

There have been rare cases of administration of botulinum toxin to patients with known or unrecognized neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. **When exposed to very high doses, patients with neurologic disorders, e.g. pediatric cerebral palsy or adult spasticity, may also be at increased risk of clinically significant systemic effects.[1]**

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX® vs. 1.2% for placebo. The most frequently reported adverse events leading to discontinuation in the BOTOX® group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%).[1]

1. BOTOX® Product Monograph, October 18, 2011.

ALLERGAN PAAB



BOTOX® onabotulinumtoxinA

see prescribing information pn pages A-15 to 17



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*Fictitious patient. May not be representative of all fibromyalgia cases.

# FACED WITH PAIN*

IN HER STRUGGLE WITH FIBROMYALGIA

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First treatment indicated in Canada for adults for the management of pain associated with **fibromyalgia**[1]

Pregabalin: first-line treatment for chronic **neuropathic pain**[2]

# DEMONSTRATED SIGNIFICANT RELIEF IN PAIN AND PAIN-RELATED SLEEP DIFFICULTIES IN FIBROMYALGIA[1]

## Demonstrated powerful, rapid and sustained pain relief[1,3-5]

**In fibromyalgia:**

- In a 14 week study, LYRICA demonstrated significant pain reduction as early as week 1 ($p<0.05$ for all doses). Mean changes in pain scores at the end of the study for LYRICA-treated patients were significantly greater versus placebo (300 mg/day, n=183: -1.75, $p=0.0009$; 450 mg/day, n=190: -2.03, $p<0.0001$; 600 mg/day, n=188: -2.05, $p<0.0001$; placebo, n=184: -1.04)[3]
- In another study of 26 weeks' duration of patients who initially responded to LYRICA during a 6-week, open-label phase, 68% of those who continued on their optimized dose (n=279) maintained a treatment response versus 39% of those on placebo (n=287). The time to loss of therapeutic response was longer in the LYRICA group ($p<0.0001$)[4]

**Also in neuropathic pain (NeP):**

- Sustained pain relief (starting at week 2 for LYRICA 150-600 mg/day, n=141; $p<0.05$ vs placebo, n=65) was demonstrated throughout a 12 week study in patients with DPN or PHN[5]

## Demonstrated effective in relieving pain-related sleep difficulties[1,6]

**In fibromyalgia:**

- In a 13 week study, LYRICA reduced overall MOS-Sleep Scale scores significantly more at the end of the study vs. placebo (300 mg/day -19.1, $p=0.0174$; 450 mg/day: -20.41, $p=0.0026$; 600 mg/day: -19.49, $p=0.0101$; placebo: -14.29)[6]

**Also in NeP:**

- LYRICA reduced sleep disturbances across several studies in DPN and PHN, of 8-12 weeks duration[1]

## Flexible dosing across all indications[1†]

LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN) and spinal cord injury in adults. LYRICA may be useful in the management of central neuropathic pain in adults. LYRICA is indicated for the management of pain associated with fibromyalgia in adults. The efficacy of LYRICA in the management of pain associated with fibromyalgia for up to 6 months was demonstrated in a placebo-controlled trial in patients who had initially responded to LYRICA during a 6-week open-label phase.

LYRICA is contraindicated in patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

The most commonly observed adverse events (≥5% and twice the rate as that seen with placebo) in the recommended dose range of 150 mg/day to 600 mg/day in PHN and DPN patients were: dizziness (9.0-37.0%), somnolence (6.1-24.7%), peripheral edema (6.1-16.2%), and dry mouth (1.9-14.9%) and were dose related; in spinal cord injury patients: somnolence (41.4%), dizziness (24.3%), asthenia (15.7%), dry mouth (15.7%), edema (12.9%), constipation (12.9%), amnesia (10.0%), myasthenia (8.6%), amblyopia (8.6%), and thinking abnormal (8.6%); in fibromyalgia patients: dizziness (37.5%), somnolence (18.6%), weight gain (10.6%), dry mouth (7.9%), blurred vision (6.7%), and peripheral edema (6.1%). In LYRICA-treated fibromyalgia patients, the most commonly observed dose-related adverse events were: dizziness (22.7-46.5%), somnolence (12.9-20.7%), weight gain (7.6-13.7%), peripheral edema (5.3-10.8%). The most commonly observed adverse events in the PHN, DPN, spinal cord injury and fibromyalgia patients were usually mild to moderate in intensity. Discontinuation rates due to adverse events for LYRICA and placebo, respectively, were 9% and 4% in DPN, 14% and 7% in PHN, 21% and 13% in spinal cord injury, and 20% and 11% in fibromyalgia. There was a dose-dependent increase in rate of discontinuation due to adverse events in fibromyalgia.

There have been post-marketing reports of angioedema in patients, some without reported previous history/episodes, including life-threatening angioedema with respiratory compromise. Caution should be exercised in patients with previous history/episodes of angioedema and in patients who are taking other drugs associated with angioedema.

In clinical trials and in post-marketing experience, there have been reports of patients, with or without previous history, experiencing renal failure alone or in combination with other medications. Caution is advised when prescribing to the elderly or those with any degree of renal impairment.

There have been post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, and constipation) in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA, primarily in combination with other medications that have the potential to produce constipation. Some of these events were considered serious and required hospitalization. In a number of instances, patients were taking opioid analgesics including tramadol. Caution should be exercised when LYRICA and opioid analgesics are used in combination, and measures to prevent constipation may be considered, especially in female patients and elderly as they may be at increased risk of experiencing lower gastrointestinal-related events.

**Dosage reduction is required in patients with renal impairment (creatinine clearance <60 mL/min) and in some elderly patients as LYRICA is primarily eliminated by renal excretion.**

Please see Prescribing Information for complete Warnings and Precautions, Adverse Reactions, Dosage and Administration and patient selection criteria.

† Please consult Prescribing Information for complete Dosage and Administration instructions.

Pfizer Working together for a healthier world™



Pr LYRICA® PREGABALIN

See prescribing information and study parameters on pages A-13, A-14

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**La Société Canadienne de Neurochirurgie**

**The Canadian Society of Clinical Neurophysiologists**
**La Société Canadienne de Neurophysiologie Clinique**

**The Canadian Association of Child Neurology**
**L'Association Canadienne de Neurologie Pédiatrique**

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Le secrétariat des quatre associations et du Fédération des sciences neurologiques du Canada est situe en permanence à:

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VIMPAT® (lacosamide) is indicated as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy (≥18 years of age) who are not satisfactorily controlled with conventional therapy. The clinical experience with VIMPAT® in elderly patients with epilepsy (≥65 years of age) is limited. Caution should be exercised during dose titration and age-associated decreased renal clearance should be considered in elderly patients. The safety and efficacy of VIMPAT® in pediatric patients (<18 years of age) have not been established and its use in this patient population is not indicated.

VIMPAT® is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients and in patients with a history of, or presence of, second- or third-degree atrioventricular (AV) block.

Second degree or higher AV block has been reported in post-marketing experience. Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheadedness and fainting), and told to contact their physician should any of these symptoms occur. VIMPAT® should be used with caution in patients with known conduction problems (e.g. marked first-degree AV block, sick sinus syndrome without pacemaker), or with a history of severe cardiac disease such as myocardial ischemia or heart failure. In such patients, obtaining an ECG before beginning VIMPAT®, and after VIMPAT® is titrated to steady-state, is recommended. Caution should especially be exerted when treating elderly patients as they may be at increased risk of cardiac disorder or when VIMPAT® is given with other drugs that prolong the PR interval (e.g. carbamazepine, pregabalin, lamotrigine, beta-blockers, and class I antiarrhythmic drugs), as further PR prolongation is possible. In clinical trials of healthy subjects and patients with epilepsy, VIMPAT® treatment was associated with PR interval prolongation in a dose-dependent manner. VIMPAT® administration may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease. Patients should be made aware of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath) and told to contact their physician should any of these symptoms occur. Atrial fibrillation and flutter have been reported in open-label epilepsy trials and in postmarketing experience.

Multiorgan hypersensitivity reactions (also known as Drug Rash with Eosinophilia and Systemic Symptoms, or DRESS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with anticonvulsants. If any of these hypersensitivity reactions are suspected, VIMPAT® should be discontinued and alternative treatment started.

Treatment with VIMPAT® has been associated with dizziness and ataxia, which could increase the occurrence of accidental injury or falls. Accordingly, patients should be advised not to drive a car or to operate other complex machinery or perform hazardous tasks until they are familiar with the effects of VIMPAT® on their ability to perform such activities.

In controlled trials in patients with partial-onset seizures, VIMPAT® treatment was associated with vision-related adverse events such as blurred vision and diplopia. Patients should be informed

ucb

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PAAB

A-8

# When seizure control is still an issue for your patient

## Bring VIMPAT® into the picture

**Efficacy in patients inadequately controlled on 1 to 3 AEDs*†[1]**

- Significant median **36-39% reduction in seizure frequency** per 28 days from baseline to maintenance phase*[1]
  - VIMPAT® 400 mg/day vs. placebo: Ben-menachem, *et al.* (39% vs. 10%, $p \leq 0.01$); Chung, *et al.* (37.3% vs. 20.8%, $p \leq 0.01$); Halász, *et al.* (36.4% vs. 20.5%, $p \leq 0.05$)*[1]

**Generally well tolerated when added to common concomitant therapy**

- Some of the most frequently reported **adverse reactions** with VIMPAT® 400 mg/day were dizziness (30%), nausea (11%), and vision-related events, including diplopia (10%) and blurred vision (9%)

The recommended starting dose for VIMPAT® is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. Depending on patient response and tolerability, the maintenance dose of VIMPAT® can be increased by 50 mg twice daily every week, to a **maximum recommended dose of 400 mg/day**.[1]

Please consult product monograph for complete dosing and administration instructions.

## POWER for added control.

that if visual disturbances occur, they should notify their physician promptly. If visual disturbance persists, further assessment, including dose reduction and possible discontinuation of VIMPAT®, should be considered.

More frequent assessments should be considered for patients with known vision-related issues or those who are already routinely monitored for ocular conditions.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

There are no studies with VIMPAT® in pregnant women. Since the potential risk for humans is unknown, VIMPAT® should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. It is unknown whether VIMPAT® is excreted in human breast milk. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue VIMPAT®, taking into account the importance of the drug to the mother.

As with all antiepileptic drugs, VIMPAT® should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency.

In controlled clinical trials in patients with partial-onset seizures, some of the most frequently reported adverse reactions with VIMPAT® treatment were dizziness (16% and 30% for 200 mg and 400 mg treatment groups, respectively, vs. 8% placebo), nausea (7% and 11% vs. 4%), and vision related events [diplopia (6% and 10% vs. 2%) and blurred vision (2% and 9% vs. 3%)]. They were dose-related and usually mild to moderate in intensity. The adverse events most commonly leading to discontinuation were dizziness, coordination abnormal, vomiting, diplopia, nausea, vertigo, and vision blurred.

Please see the VIMPAT® Product Monograph for full prescribing information.

* 3 randomized, double-blind, placebo-controlled, multicentre trials studying VIMPAT® (lacosamide) as adjunctive therapy in adult patients with POS with or without secondary generalization. In the studies, patients were to have been taking a stable dosage regimen of one to three AEDs, with or without vagal nerve stimulation in the 4 weeks before enrollment and during the baseline period. Following the 8-week baseline phase, subjects were randomized and up-titrated by initiating treatment at 100 mg/day, and increased in weekly increments of 100 mg/day to the target dose. The titration phase lasted 4-6 weeks. Patients then entered a 12-week maintenance phase period.[2,3,4]

† AED=anti-epileptic drug

**References:** 1. VIMPAT® Product Monograph, UCB Canada Inc., October 6, 2011. 2. Ben-Menachem E, Biton V, Jatuzis D, *et al.* Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; 48(7):1308-1317. 3. Chung S, Sperling MR, Biton V *et al.* Lacosamide as adjunctive therapy for partial onset seizures: A randomized controlled trial. *Epilepsia* 2010; 51(6):958-967. 4. Halász P, Kalviainen R, Mazurkiewicz-Beldzińska M, *et al.* Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. *Epilepsia* 2009; 50(3):443-453.

℞ VIMPAT™
lacosamide

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See prescribing summary on page A-18 to A-21

# Professionals Need Dedicated Advice to 'Catch Up' on Building and Preserving Wealth

Life doesn't slow down for today's professionals, who shift from years of intensive study into busy careers, devoting long hours to caring for others and juggling the business side of their practice.

While they enjoy the pace and rewards of their field, it's critical for these professionals to also pay attention to their changing wealth management needs, in light of their unique financial circumstances.

"Professionals often begin their careers later than others," observes John Roberts, Vice President, Small Business Banking, Scotiabank. "This means that from the moment their income begins to rise, they need to play catch-up on building wealth for the future. This is not always easy, since they may be saddled with debt, eager to move forward with many personal and professional goals, yet time-pressed to do it all."

Fortunately, it is possible to balance competing goals – even pay down student debt within two years and accumulate an investment portfolio – if a professional enlists the right advisor and develops a financial plan to chart their path from cash-strapped to cash laden.

And the need for solid advice continues over a professional's 'compressed' career, since they must make key financial decisions, and consider tax issues, at each stage of their working life. For example, as a practice matures, a professional needs a strategy to create wealth, manage it and preserve it through Will and estate planning and charitable giving. While professionals typically have a lawyer or an accountant to handle immediate needs, they often lack a comprehensive financial plan and partner to come to an integrated view of their long-term goals.

"Professionals require customized financial advice that will help them anticipate their needs, and think two steps ahead. They may want to discuss borrowing to buy equipment or a boat, but we can help them grow their practice, invest for the future and structure their retirement or pension plan," explains Mr. Roberts, adding that a thorough succession plan should begin at least five years before a professional aims to retire.

Mr. Roberts notes that Scotiabank offers solutions geared to each stage of a professional's career, from in-branch advisors, to specialist wealth partners in investment management, estate and trust planning, private banking and insurance strategies plus self-directed investing with Scotiabank iTRADE. Exclusive discounts and reduced fees are available as part of the Scotia Professional Plan.

"As busy as professionals are, it's critical to be proactive getting your total financial picture in order," concludes Mr. Roberts. "With the right advice and attention to your needs, you can concentrate on your practice, while your money works just as hard for you to create long-term wealth." Contact a Scotiabank branch representative for an introduction to a Scotia Private Client Group wealth management specialist or see a Small Business Advisor for more details.

**Scotia Professional Plan**

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