INFORMATION FOR AUTHORS SUBMISSION PROCESS

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- Provide a table number and title for each.
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- Place explanatory matter in footnotes, not in the heading.
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Journals

1. Rose ME, Huerbin MB, Melick J, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Chapter in a book

1. Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

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https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

PrLYRICA® PREGABALIN

PRESCRIBING SUMMARY

PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION
Analgesic Agent

INDICATIONS AND CLINICAL USE
LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia and spinal cord injury. LYRICA is indicated for the management of pain associated with fibromyalgia. 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.

Use in Special Populations
Geriatrics (>65 years of age): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see *WARNINGS AND PRECAUTIONS, Geriatrics* [*>65 years of age*]).

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established.

Renal: There have been reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregab alin showed reversibility of this event in some cases (see Product Monograph, *WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions; and DOSAGE AND ADMINISTRATION*). Because pregabalin is eliminated primarily by renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients or those with renal impairment (see Product Monograph, *ACTION AND CLINICAL PHARMACOLOGY* and *DOSAGE AND ADMINISTRATION*).

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labour and Delivery: The effects of pregabalin on labour and delivery in pregnant women are unknown.

Nursing Women: It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

CONTRAINDICATIONS
Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Angioedema: There have been post-marketing reports of angioedema in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), neck, throat, and larynx/upper airway. There have been reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Some of these patients did not have reported previous history/episode(s) of angioedema. LYRICA should be immediately discontinued in patients with these symptoms. During the pre-marketing assessment of pregabalin in clinical trials, angioedema was reported as a rare reaction (see Product Monograph, *ADVERSE REACTIONS*, Less Common Clinical Trial Adverse Reactions and Post-Marketing Adverse Drug Reactions). Caution should be exercised when prescribing LYRICA to patients with previous history/episode(s) of angioedema and related events. In addition, patients who are taking other drugs associated with angioedema (eg, ACE-inhibitors) may be at increased risk of developing this condition.

Hypersensitivity: There have been post-marketing reports of hypersensitivity reactions (e.g. skin redness, blisters, hives, rash, dyspnea, and wheezing). Pregabalin should be discontinued immediately if such symptoms occur (see Product Monograph, Post-Marketing Adverse Drug Reactions).

Renal Failure: In both clinical trials of various indications and post-marketing database, there are reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Caution is advised when prescribing pregabalin to the elderly or those with any degree of renal impairment (see Product Monograph, Special Populations, *Renal;* Abrupt or Rapid Discontinuation; *ADVERSE REACTIONS*, Post-Marketing Adverse Drug Reactions; and *DOSAGE AND ADMINISTRATION*).

Tumorigenic Potential: In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Ophthalmological Effects: In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see Product Monograph, *Post-Marketing Adverse Drug Reactions*).

Patients should be informed that if changes in vision occur, they should notify their physician.

Peripheral Edema: LYRICA may cause peripheral edema. In controlled peripheral neuropathic pain and fibromyalgia clinical trials, pregabalin treatment caused peripheral edema in 9% of patients compared with 3% of patients in the placebo group. In these studies, 0.7% of pregabalin patients and 0.3% of placebo patients withdrew due to peripheral edema (see Product Monograph, *ADVERSE REACTIONS, Peripheral Edema*).

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Congestive Heart Failure: In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate (between 0.1% and 1%; see Product Monograph, *ADVERSE REACTIONS*, Less Common Clinical Trial Adverse Reactions).

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see Product Monograph, *ADVERSE REACTIONS*, Post-marketing Adverse Drug Reactions). Although this adverse reaction has mostly been observed in elderly cardiovascular-compromised patients during pregabalin treatment for a neuropathic pain indication, some cases have occurred in patients without reported edema or previous history of cardiovascular disease. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Gastrointestinal: There have been post-marketing reports of events related to reduced lower gastrointestinal tract function (eg. 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 (see Product Monograph, *ADVERSE REACTIONS*, Post-Marketing Adverse Drug Reactions).

Weight Gain: LYRICA may cause weight gain. In pregabalin-controlled peripheral neuropathic pain and fibromyalgia clinical trials with durations of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 3% of placebo-treated patients. Few patients treated with pregabalin (0.6%) withdrew from controlled trials due to weight gain (see Product Monograph, *ADVERSE REACTIONS*, Weight Gain).

Pregabalin-associated weight gain was related to dose and duration of exposure. Pregabalin-associated weight gain did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema and was not necessarily due to edema-related events (see Product Monograph, *WARNINGS AND PRECAUTIONS*, Peripheral Edema).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open-label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}).

Dizziness and Somnolence: LYRICA may cause dizziness and somnolence. In controlled studies, pregabalin caused dizziness in 32% of patients compared to 8% in placebo. Somnolence was experienced by 17% and 4% of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses. In these studies, dizziness and somnolence led to withdrawal of 5% (placebo: 0.5%) and 3% (placebo: 0.1%) of the pregabalin-treated patients, respectively. For the remaining patients who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 35% and 49% of the patients, respectively (see Product Monograph, *ADVERSE REACTIONS*, Tables 2, 4, and 11, and Post-Marketing Adverse Drug Reactions).

Abrupt or Rapid Discontinuation: Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see Product Monograph, *ADVERSE REACTIONS, Adverse Events Following Abrupt or Rapid Discontinuation*).

ADVERSE REACTIONS
Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trial Adverse Drug Reactions
Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Neuropathic Pain: The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema, and dry mouth. Adverse events were usually mild to moderate in intensity.

Adverse Events from a Controlled Clinical Study in Neuropathic Pain Associated with Spinal Cord Injury: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: somnolence, dizziness, asthenia, dry mouth, edema, myasthenia, constipation, thinking abnormal, amblyopia, and amnesia. Adverse events were usually mild to moderate in intensity.

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

Most Common Adverse Events in Controlled Clinical Studies in Fibromyalgia: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness (37.5%), somnolence (18.6%), weight gain (10.6%), dry mouth (7.9%), blurred vision (6.7%), peripheral edema (6.1%), constipation (5.8%), and disturbance in attention (5.3%). Adverse events were usually mild to moderate in intensity.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect a patient has had a serious or unexpected reaction to this drug, you may notify Health Canada by telephone: 1-866-234-2345.

ADMINISTRATION

DOSING CONSIDERATIONS

Patients with Impaired Renal Function

Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In some elderly patients and those with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in Supplemental Product Information).

Adults

Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently (see Product Monograph, *ADVERSE REACTIONS*, Tables 1 and 5). Doses above 600 mg/day have not been studied and are not recommended.

Neuropathic pain associated with spinal cord injury: The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered. Doses above 600 mg/day have not been studied and are not recommended.

Pain associated with fibromyalgia: The recommended dosage is 300 to 450 mg/day, given in two divided doses. The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Based on individual response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg BID (450 mg/day). In some patients, efficacy of LYRICA has been demonstrated within the first week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials of fibromyalgia, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced significantly higher rates of adverse events and discontinued the trial more frequently (see Product Monograph, *ADVERSE REACTIONS*, Tables 7 and 10). In view of the dose-related adverse events, the decision to treat patients with doses above 450 mg/day should be based on clinical judgment of the treating physician. Doses above 600 mg/day have not been studied and are not recommended.

ADMINISTRATION

LYRICA is given orally with or without food.

STUDY REFERENCES

References:

1. LYRICA Product Monograph, Pfizer Canada Inc., June 21, 2010.
2. Moulin DE *et al.* Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12:13-21.
3. Arnold LM *et al.* A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain* 2008;9:792-805.

   14-week, randomized, double-blind, multiple-dose, placebo-controlled, multicentre study. 745 patients who had moderate-to-severe pain, i.e. mean baseline score (mean of the last 7 daily diary pain scores prior to study medication) of ≥4, and a diagnosis of fibromyalgia based on the ACR criteria. This study used an enriched population as placebo responders (≥30% reduction in mean pain scores) during the one-week run-in phase were discontinued and did not enter the double-blind phase. 1.6% of patients screened (n=19/1,195) were reported to be placebo responders. Patients were randomized to LYRICA 300 mg/day (n=183), 450 mg/day (n=190), 600 mg/day (n=188), or placebo (n=184). Patients were allowed to take acetaminophen up to 4 g/day as needed for pain relief. The number of completers was: LYRICA 300 mg/day (n=123), 450 mg/day (n=125), 600 mg/day (n=113), or placebo (n=125). The primary endpoint was the reduction in endpoint mean pain scores. Pain scores rated on 11-point numerical scale from 0 (no pain) to 10 (worst possible pain) during the past 24 hours. Mean baseline pain scores were 6.7 for LYRICA 300 mg/day, 6.7 for 450 mg/day, 6.8 for 600 mg/day, and 6.6 for placebo.
4. Crofford LJ *et al.* Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008;136:419-31.

   26-week, long-term relapse observation study. Patients who met the ACR criteria for fibromyalgia and who had a score of ≥40 on the pain Visual Analog Scale (VAS) were eligible to enter a 6-week, open-label, dose-optimization phase. During this phase, patients were titrated up to a total daily dose of 300 mg, 450 mg, or 600 mg. 566 LYRICA responders were randomized in the double-blind phase to either their optimized LYRICA dose (n=279) or to placebo (n=287). 38% of LYRICA responders completed 26 weeks of treatment vs 19% on placebo. The primary endpoint was time to loss of therapeutic response. Loss of therapeutic response was defined as having either a <30% reduction in pain VAS score, or worsening of symptoms necessitating alternate treatment. Responders were defined as having a ≥50% reduction in pain on the VAS and self-rating on the Patient Global Impression of Change scale of "much improved" or "very much improved".
5. Freynhagen R *et al.* Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005;115:254-63.

   In a 12-week, multicentre, randomized, double-blind, placebo-controlled study, 338 patients with either DPN (n=249) or PHN (n=89) were randomized to receive BID flexible-dose pregabalin (150-600 mg/day), fixed-dose pregabalin (600 mg/day) or placebo. In the flexible-dose arm, dose could be adjusted up or down over the first four weeks based on patients' individual response and tolerability. The primary efficacy measurement was mean pain score at endpoint, derived from ratings recorded by patients in a daily diary on an 11-point numerical pain rating scale (0=no pain, 10=worst possible pain). A significant difference in pain scores versus placebo was seen in the flexible dose range 150-600 mg/day ($p \leq 0.05$, weeks 2-3 and $p \leq 0.01$, weeks 4-12), and the fixed dose of 600 mg/day ($p \leq 0.05$, week 1 and $p \leq 0.01$, weeks 2-12).
6. Mease PJ *et al.* A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008;35:502-14.

   Multicentre, double-blind, 13-week, randomized trial. 748 patients who met the ACR criteria for fibromyalgia and who had an average mean pain score of ≥4 on an 11-point numeric rating scale (NRS) during the baseline assessment were randomized to LYRICA 300 mg/day (n=185), 450 mg/day (n=183), 600 mg/day (n=190), or placebo (n=190). Patients were allowed to take acetaminophen up to 4 g/day as needed for pain relief. The number of completers was: LYRICA 300 mg/day (n=123), 450 mg/day (n=121), 600 mg/day (n=111), or placebo (n=130). The primary endpoint was the reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Pain-related sleep difficulties were assessed using the Medical Outcomes Study-Sleep Scale (MOS-SS), a scale that runs from 0-100. Mean baseline MOS-SS score for overall sleep problem index was 65.0.

SUPPLEMENTAL PRODUCT INFORMATION

Warnings and Precaution

See the Product Monograph for further information on the following: tumorigenic potential, ophthalmological effects, peripheral edema, congestive heart failure, weight gain, dizziness and somnolence, sexual function/reproduction, and special populations.

Drug Interactions

Overview: Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (≤2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Drug Abuse and Dependence/Liability: Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

ADMINISTRATION

Dosage Adjustment Based on Renal Function: Dosing adjustment should be based on creatinine clearance (Cl_{cr}), as indicated in Table 1.

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table below).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a] Recommended Dose Escalation*				Dose Regimen
	Starting dose	→ up to		Maximum daily dose	
≥60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
<15	25	25-50	50-75	75	QD
Supplementary dosage following hemodialysis (mg)[b]					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50-75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.
* Based on individual patient response and tolerability.
[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
[b] Supplementary dose is a single additional dose.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans: The highest known dose of pregabalin received in the clinical development program in which there was no fatal outcome was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin. In post-marketing experience, fatal outcomes in cases in which pregabalin has been taken in combination with other medications have been reported with a pregabalin overdose as low as 800 mg in a day. In none of these cases has pregabalin been established as the cause of death or in pregabalin monotherapy. The lowest fatal dose with pregabalin alone has not yet been identified.

The most commonly reported adverse events observed when pregabalin was taken in overdose (dose range from 800 mg/day up to 11,500 mg as a single dose) included affective disorder, somnolence, confusional state, depression, agitation, and restlessness.

Treatment or Management of Overdose: There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Hemodialysis: Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

Availability of Dosage Forms

LYRICA is available in dosage strengths of 25 mg, 50 mg, 75 mg, 100 mg*, 150 mg, 200 mg*, 225 mg, and 300 mg capsules.

* Not commercially available in Canada

For a copy of the Product Monograph or full Prescribing Information, please contact: Pfizer Canada Medical Information at 1-800-463-6001 or visit www.pfizer.ca.

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https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

BOTOX®
onabotulinumtoxinA

onabotulinumtoxinA for injection Ph. Eur.
Clostridium botulinum type A neurotoxin complex (900kD)
Sterile vacuum-dried concentrate powder for solution for injection
50, 100 and 200 Allergan units per vial

Prescribing Summary

Patient Selection Criteria

Neuromuscular Paralytic Agent

INDICATIONS

BOTOX® (onabotulinumtoxinA for injection) is indicated:

- for prophylaxis of headaches in adults with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

CONTRAINDICATIONS

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. For a complete listing of the ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.
- the presence of infection at the proposed injection site(s).

USE IN SPECIAL POPULATIONS

Pregnant Women: There are no adequate and well-controlled studies of BOTOX® administration in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. BOTOX® should not be used during pregnancy unless clearly necessary. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX® is administered to a nursing woman.

Pediatrics (2–18 years of age): There have been very rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. A causal association to BOTOX® has not been established in these cases. Post-marketing reports of possible distant spread of toxin have been very rarely reported in pediatric patients with co-morbidities, predominantly with cerebral palsy, who received >8 U/kg. Extreme caution should be exercised when treating pediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

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.

Geriatrics (> 65 years of age): Studies specifically designed to determine dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. Initial dosing should begin at the lowest recommended dose for the specific indication.

The safety and effectiveness of BOTOX® in the prophylaxis of headaches in chronic migraine has not been investigated in subjects over 65 years of age.

Safety Information

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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.
- 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®. (See WARNINGS AND PRECAUTIONS, General, and DOSAGE AND ADMINISTRATION).

General

Use BOTOX® only as directed.

Do not use dosage recommendations and potency Units applied to other botulinum toxin products when using BOTOX®.

The safe and effective use of BOTOX® (onabotulinumtoxinA for injection) depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.

Physicians administering BOTOX® should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for treatment of strabismus, and may be useful for the treatment of cervical dystonia, and focal spasticity associated with pediatric cerebral palsy and upper limb spasticity in adults.

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.

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.

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

Patients with a history of underlying neurological disorders, dysphagia and/or aspiration should be treated with extreme caution. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk.

Injection specific dosage and administration recommendations should be followed. In treating adult patients, including when combining indications, the maximum cumulative dose should generally not exceed 360 Units, up to a maximum of 6 U/kg, in a 3 month interval. In treating pediatric patients, the maximum cumulative dose should generally not exceed 6 Units/kg, up to a maximum of 200 Units, in a 3 month interval.

The primary release procedure for BOTOX® uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's product BOTOX®. One Allergan Unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX® is approximately 20 Units/nanogram of neurotoxin protein complex.

This product contains human serum albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy – BOTOX® is a treatment of spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX® is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

No efficacy has been shown for BOTOX® in the prophylaxis of headaches in patients with episodic migraine (< 15 headache days per month).

Carcinogenesis and Mutagenesis

Studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX®. BOTOX® was not mutagenic in *in vitro* and *in vivo* mutagenicity studies.

Cardiovascular

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.

Ear/Nose/Throat

Cervical Dystonia—Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all types of botulinum toxins. Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be mild, but could be severe. Consequent to the dysphagia there is the potential for aspiration, dyspnea and occasionally the need for tube feeding. In rare cases, dysphagia followed by aspiration pneumonia and death has been reported.

Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia has contributed to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX® injection.

Limiting the dose injected into both sternocleidomastoid muscles to less than 100 units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the localized diffusion of the toxin to the oesophageal musculature.

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

Immune

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX® treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

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

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent for BOTOX® and consequently the causal agent cannot be reliably determined. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately.

Neurologic

Extreme caution should be exercised when administering BOTOX® to individuals with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX®. 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.**

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The reports in children were reports predominantly from cerebral palsy patients treated for spasticity. The exact relationship of these events to the botulinum toxin injection has not been established.

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

Skin

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope. Care should be taken when injecting near vulnerable anatomic structures.

Primary hyperhidrosis of the axillae—Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism or phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

ADVERSE REACTIONS

Adverse Events Reaction Overview

In general, adverse reactions occur within the first few days following injection and while generally transient may have duration of several months or, in rare cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported. 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, some associated with a fatal outcome.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Post-market Adverse Drug Reactions:

BOTOX® and BOTOX COSMETIC® contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of BOTOX COSMETIC® also have the potential to be associated with the use of BOTOX®.

Adverse events after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, respiratory compromise, pneumonia, and/or other significant debility. There have also been rare reports 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. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

The following other adverse events have been reported since the drug has been marketed: abdominal pain; diarrhea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance, hypoacusis; tinnitus; vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoaesthesia; malaise; myalgia; myasthenia gravis; paraesthesia; allergic reaction, skin rash (including erythema multiforme, urticaria and psoriasiforme eruption); pruritus; hyperhidrosis; alopecia, including madarosis.

Angle closure glaucoma has been reported very rarely following BOTOX® treatment for blepharospasm.

These reactions are reported voluntarily from a population of uncertain size. The exact relationship of these events to botulinum toxin is unknown.

DRUG INTERACTIONS

Overview

No specific interactions have been reported.

Drug-Drug Interactions

Table 1: Established or Potential Drug-Drug Interactions

Proper name of drug	Ref	Effect	Clinical comment
Aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents, both depolarizing (succinylcholine) and non-depolarizing (tubocurarine derivatives), lincosamides, polymyxins, quinidine, magnesium sulfate, and anticholinesterases).	T	Theoretically, the effect of botulinum toxin type A may be potentiated	The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other drugs that interfere with neuromuscular transmission (e.g. tubocuraine-type muscle relaxants). Caution should be exercised when BOTOX® is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs that interfere with neuromuscular transmission.
Different botulinum neurotoxin serotypes	T	Unknown	The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Legend: T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

To report an adverse effect to Allergan Inc., please call 1-800-433-8871.

Administration

Dosing Considerations

- **Intramuscular Use for All Indications except Hyperhidrosis**
- **Intradermal Use for Hyperhidrosis only**
- BOTOX® (onabotulinumtoxinA for injection) should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.
- 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.
- The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative.
- Follow the recommended dosage and frequency of administration for each indication.
- Generally, optimum dose levels and the number of injection sites per muscle have not been established for all indications. Treatment should be initiated at the lowest effective dose. This dose can be gradually increased in subsequent treatments to the maximum recommended dose, if needed.
- Injection intervals of BOTOX® should be according to the specific indication. In treating adult patients, when combining indications, the maximum cumulative dose should generally not exceed 6 Units/kg, up to a maximum of 360 Units, in a 3 month interval. In treating pediatric patients, the maximum cumulative dose should generally not exceed 6 Units/kg, up to a maximum of 200 Units, in a 3 month interval.

Recommended Dose and Dosage Adjustment

Chronic Migraine:

The recommended dilution is 200 U/4 mL or 100 U/2 mL, with a final concentration of 5 U per 0.1 mL (see Dilution Table 5). The recommended dose for treating chronic migraine is 155 U administered intramuscularly (IM) as 0.1 ml (5 U) injections to 31 sites using a 30-gauge, 0.5 inch needle. Injections should be divided across 7 specific head/neck muscle areas as specified in Table 2 below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated below, with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), optional additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle (Table 2). This represents a total maximum dose for chronic migraine of 195 U (39 sites).

The recommended retreatment schedule is every 12 weeks.

Table 2: BOTOX® Dosing By Muscle for Chronic Migraine

	Recommended Dose
Head/Neck Area	Total Number of Units (U) (number of IM injection sites[a])
Frontalis[b]	20 U (4 sites)
Corrugator[b]	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis[b]	30 U (6 sites) up to 40 U (up to 8 sites)
Temporalis[b]	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius[b]	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical paraspinal group[b]	20 U (4 sites)
Total Dose:	155 U to 195 (31 to 39 sites)

[a] 1 IM injection site = 0.1 mL = 5 U BOTOX®.
[b] Dose distributed bilaterally for minimum dose.

Lack of Response:

There are several potential explanations for a lack of or diminished response to an individual treatment with BOTOX®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement, patient perception of benefit compared with initial results, inappropriate storage or reconstitution, as well as neutralizing antibodies to botulinum toxin. A neutralizing antibody is defined as an antibody that inactivates the biological activity of the toxin. However, there have been patients who continued to respond to therapy and demonstrated presence of neutralizing antibodies; the proportion of patients which lose their response to botulinum toxin therapy and have demonstrable levels of neutralizing antibodies is small.

To reduce the potential for neutralizing antibody formation, it is recommended that injection intervals should be no more frequent than two months. In general, the dose should not exceed 360 U in any two month period. No patients among 496 chronic migraine patients with analyzed specimens showed the presence of neutralizing antibodies.

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

A suggested course of action when patients do not respond to BOTOX® injections is:

1) wait the usual treatment interval;
2) consider reasons for lack of response listed above;
3) more than one treatment course should be considered before classification of a patient as a non-responder;
4) test patient serum for neutralizing antibody presence.

Missed Dose

Missed doses may be administered as soon as is practical.

Administration

An injection of BOTOX® is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe may be attached to the electromyographic injection needle, preferably a 1.5 inch, 27 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new sterile needle and syringe should be used to enter the vial or each occasion for dilution or removal of BOTOX®.

Reconstitution:

Parenteral Products:
To reconstitute vacuum-dried BOTOX®, use sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX® is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX® should be administered within twenty-four hours after reconstitution.

During this time period, reconstituted BOTOX® should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX® should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

Table 5: Dilution

Quantity of Diluent Added (0.9% Sodium Chloride Injection)	Resulting dose Units per 0.1 mL		
	50 U Vial	100 U Vial	200 U Vial
1.0 mL	5.0 U	10.0 U	20.0 U
2.0 mL	2.5 U	5.0 U	10.0 U
4.0 mL	1.25 U	2.5 U	5.0 U
8.0 mL	–	1.25 U	2.5 U

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX® dose is also possible by administering a smaller or larger injection volume (i.e., 0.05 mL [50% decrease in dose] to 0.15 mL [50% increase in dose]).

Study References

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

Supplemental Product Information

Adverse Reactions:

For each indication the frequency of adverse reactions documented during clinical trials is given. The following lists events that occurred in ≥ 1% of subjects. The frequency is defined as follows: Very Common (≥1/10); Common (≥1/100, <1/10).

Chronic Migraine
Safety data compiled from two chronic migraine double-blind, placebo controlled phase 3 clinical trials involving 687 patients treated with BOTOX®. The following adverse reactions were reported.

Adverse Events Reported by ≥ 2% of BOTOX®-Treated Patients and More Frequent than in Placebo-treated Patients in Two Phase 3 Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

System Organ Class/ Preferred Term	BOTOX® (N = 687)	Placebo (N = 692)
Overall	429 (62.4%)	358 (51.7%)
Eye Disorders		
Eyelid ptosis	25 (3.6%)	2 (0.3%)
General Disorders & Administration Site Conditions		
Injection site pain	23 (3.3%)	14 (2.0%)
Infections & Infestations		
Sinusitis	28 (4.1%)	27 (3.9%)
Bronchitis	17 (2.5%)	11 (1.6%)
Musculoskeletal & Connective Tissue Disorders		
Neck pain	60 (8.7%)	19 (2.7%)
Musculoskeletal stiffness	25 (3.6%)	6 (0.9%)
Muscular weakness	24 (3.5%)	2 (0.3%)
Myalgia	21 (3.1%)	6 (0.9%)
Musculoskeletal pain	18 (2.6%)	10 (1.4%)
Nervous System Disorders		
Headache	32 (4.7%)	22 (3.2%)
Migraine	26 (3.8%)	18 (2.6%)
Facial paresis	15 (2.2%)	0 (0.0%)

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%).

MANAGEMENT OF OVERDOSE

For the management of a suspected drug overdose, contact your Regional Poison Control Centre

In the event of overdosage or injection error, additional information may be obtained by contacting Allergan Inc. at 1-800-433-8871.

Overdose of BOTOX® is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, or overdose be suspected, the person should be medically monitored for up to several weeks for progressive signs or symptoms of muscular weakness distant from the site of injection that may include ptosis, diplopia, swallowing and speech disorders, generalized weakness or respiratory failure. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

When used for prophylaxis of headaches in adults with chronic migraine BOTOX® may act as an inhibitor of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical stucies.

STORAGE AND STABILITY

- Store the vacuum-dried product either in a refrigerator at 2° to 8°C, or in a freezer at or below -5°C.
- Administer BOTOX® within 24 hours after the vial is removed from the freezer and reconstituted.
- During these 24 hours, reconstituted BOTOX® should be stored in a refrigerator (2° to 8°C).
- Reconstituted BOTOX® should be clear, colorless and free of particulate matter.
- Do not freeze reconstituted BOTOX®.
- At the time of use, product acceptability should be confirmed relative to the expiration date indicated on the product vial and outer box.

SPECIAL HANDLING INSTRUCTIONS

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BOTOX® is available in 50, 100 and 200 unit (U) sterile vials of *Clostridium botulinum* toxin type A in a vacuum-dried form without a preservative. One Allergan unit (U) corresponds to the calculated median lethal dose (LD_{50}) in mice using reconstituted BOTOX® and injected intraperitoneally.

The quantities of the ingredients in each vial are listed below:

INGREDIENTS	50 Allergan U Vial	100 Allergan U Vial	200 Allergan U Vial
Clostridium botulinum toxin type A neurotoxin complex (900kD)	50 U	100 U	200 U
Human Serum Albumin	0.25 mg	0.5 mg	1.0 mg
Sodium Chloride	0.45 mg	0.9 mg	1.8 mg

Complete product monograph available on request:

Allergan Inc.
85 Enterprise Blvd., Suite 500
Markham, Ontario L6G 0B5
1-800-668-6424
or visit www.allergan.ca

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ALLERGAN BOTOX® onabotulinumtoxinA PAAB

See our AD on OBC

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

PrVIMPAT™
lacosamide

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Antiepileptic Agent

INDICATIONS AND CLINICAL USE

Adults (≥18 years of age): VIMPAT (lacosamide) 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. VIMPAT (lacosamide) solution for injection for intravenous use is an alternative when oral administration is temporarily not feasible.

Geriatrics (≥65 years of age): The clinical experience with VIMPAT in elderly patients with epilepsy is limited (n=18). Caution should be exercised during dose titration and age-associated decreased renal clearance should be considered in elderly patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics, DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Pediatrics (<18 years of age): 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 (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**). Only ten pediatric patients (16 to 17 years of age) participated in controlled trials of partial-onset seizures.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance or to any of the excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Patients with a history of, or presence of, second-or third-degree atrioventricular (AV) block.

Safety Information

WARNINGS AND PRECAUTIONS

General Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, VIMPAT (lacosamide) should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency. (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**). **Cardiac Rhythm and Conduction Abnormalities PR Interval Prolongation** 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 atrioventricular (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 or beta-blockers), as further PR prolongation is possible (see **DRUG INTERACTIONS**). In clinical trials of healthy subjects and patients with epilepsy, VIMPAT treatment was associated with PR interval prolongation in a dose-dependent manner (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**). Patients with significant electrocardiographic (ECG) abnormalities were systematically excluded from these trials. The mean PR interval increase (at t_{max}) in a clinical pharmacology ECG trial of healthy subjects was 13.6ms for the 400 mg/day VIMPAT group, 18.2ms for the 800 mg/day VIMPAT group, and 6.3ms for the placebo group. The mean increase in PR interval at the end of 12 weeks maintenance treatment for patients with partial-onset seizures who participated in the controlled trials was 1.4ms, 4.4ms, and 6.6ms for the VIMPAT 200, 400, and 600 mg/day groups, respectively, and -0.3ms for the placebo group. The mean maximum increase in PR interval in these controlled trials was 12.7ms, 14.3ms, and 15.7ms in the VIMPAT 200, 400, and 600 mg/day groups and 11.2ms in the placebo group. Among patients who participated in these controlled trials, asymptomatic first-degree atrioventricular (AV) block was detected on ECG and reported as an adverse reaction for 0.4% (4/944 patients) in the VIMPAT group and 0% (0/364 patients) in the placebo group (see **ADVERSE REACTIONS**). **Atrial Fibrillation and Atrial Flutter** 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 post-marketing experience. No cases occurred in the short-term investigational trials of VIMPAT in epilepsy patients. In patients with diabetic neuropathy, 0.6% of patients treated with VIMPAT experienced an adverse reaction of atrial fibrillation or atrial flutter, compared to 0% of placebo treated patients. **Syncope** In the short-term controlled trials of VIMPAT in epilepsy patients with no significant system illnesses, there was no increase in syncope compared to placebo. In the short-term controlled trials of VIMPAT in patients with diabetic neuropathy, 1.0% of patients who were treated with VIMPAT reported an adverse reaction of syncope or loss of consciousness, compared to 0% of placebo-treated patients with diabetic neuropathy. Most of the cases of syncope were observed in patients receiving doses above 400 mg/day. The cause of syncope was not determined in most cases. However, several were associated with either changes in orthostatic blood pressure, atrial flutter/fibrillation (and associated tachycardia), or bradycardia (see **ADVERSE REACTIONS, Intravenous Adverse Reactions**). **Carcinogenesis and Mutagenesis** See **Product Monograph Part II: TOXICOLOGY, Carcinogenicity and Mutagenicity** for discussion on animal data. **Hypersensitivity** 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. Typically, although not exclusively, DRESS presents with fever and rash associated with other organ system involvement, that may or may not include eosinophilia, hepatitis, nephritis, lymphadenopathy, and/or myocarditis. Because these disorders are variable in their expression, other organ system signs and symptoms not noted here may also occur. If any of these hypersensitivity reactions are suspected, VIMPAT should be discontinued and alternative treatment started. One case of symptomatic hepatitis and nephritis was observed among 4011 subjects exposed to VIMPAT during clinical development. The event occurred in a healthy volunteer, 10 days after stopping VIMPAT treatment. The subject was not taking any concomitant medication and potential known viral etiologies for hepatitis were ruled out. The subject fully recovered within a month, without specific treatment. The case is consistent with a delayed multiorgan hypersensitivity reaction. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology. One case of SJS was reported in post-marketing experience during treatment with VIMPAT in combination with other antiepileptic drugs, but this case was not considered to be related to VIMPAT by the reporter. SJS was not reported during clinical development. No cases of TEN were reported during clinical development, and none have been reported in post-marketing experience. **Neurologic Dizziness and Ataxia** Treatment with VIMPAT has been associated with dizziness and ataxia which could increase the occurrence of accidental injury or falls. In controlled clinical trials, dizziness was experienced by 25% of patients with partial-onset seizures taking 1 to 3 concomitant AEDs randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared with 8% of placebo patients) and was the adverse event most frequently leading to discontinuation (3%). Ataxia was experienced by 6% of patients randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared to 2% of placebo patients) (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions**). There was a substantial increase in the frequency of occurrence of these events when patients received VIMPAT doses greater than 400 mg/day. 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 (see **Part III: CONSUMER INFORMATION**). **Ophthalmological Effects** In controlled trials in patients with partial-onset seizures, VIMPAT treatment was associated with vision-related adverse events such as blurred vision (VIMPAT, 8%; placebo, 3%) and diplopia (VIMPAT, 11%; placebo, 2%). Three percent of patients randomized to VIMPAT discontinued treatment due to vision-related adverse events (primarily diplopia) (see **ADVERSE REACTIONS**). Patients should be informed 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. **Psychiatric Suicidal Ideation and Behaviour** 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. An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known. There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms. **Special Populations Women of Childbearing Potential / Contraception:** There was no clinically relevant interaction between lacosamide and oral contraceptives (ethinylestradiol and levonorgestrel) in clinical studies (see **DRUG INTERACTIONS, Drug-Drug Interactions, Oral Contraceptives**). **Pregnant Women:** There are no studies with lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embyrotoxicity was observed in rats and rabbits at maternal toxic doses (see **TOXICOLOGY, Reproduction Studies**). 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. If women decide to become pregnant while taking VIMPAT, the use of this product should be carefully re-evaluated. **Pregnancy Registry:** Physicians are advised to recommend that pregnant patients taking VIMPAT enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

following website: http://www.aedpregnancyregistry.org/. **Nursing Women:** It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue lacosamide, taking into account the importance of the drug to the mother. **Fertility:** No adverse effects on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD) of 400 mg/day. **Geriatrics (≥65 years of age):** The experience withVIMPAT in elderly patients with epilepsy is limited (n=18). Although no dose reduction is necessary in elderlypatients, caution should be exercised during dose titration and age-associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations** and **Conditions, Geriatrics**). **Pediatrics (<18 years of age):** VIMPAT is not indicated for use in pediatrics (<18 years of age) as there is insufficient data on safety and efficacy of the drug in this population (see **INDICATIONS and DOSAGE AND ADMINISTRATION**). **Monitoring and Laboratory Tests** See **WARNINGS AND PRECAUTIONS, Cardiac Rhythm and Conduction Abnormalities. Adverse Drug Reaction Overview**

In controlled clinical trials in patients with partial-onset seizures, 924 patients received VIMPAT (lacosamide). Some of the most frequently reported adverse reactions in controlled clinical trials with lacosamide treatment were dizziness, nausea, and vision-related events (e.g. diplopia, blurred vision). They were dose-related and usually mild to moderate in intensity. **Clinical Trial Adverse Drug Reactions** *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trialsis useful for identifying drug-related adverse events and for approximating rates.* Table 1 gives the incidence of treatment-emergent adverse events that occurred in ≥1% of adult patients with partial-onset seizures in the total VIMPAT group (n=944) and for which the frequency was greater than placebo, in controlled clinical trials. The majority of adverse events were reported with a maximum intensity of 'mild' or 'moderate'.

Table 1: Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events ≥1% of Patients in the total VIMPAT group and More Frequent Than in the Placebo Group).

MedDRA System Organ Class/ Preferred Term	Placebo N=364 %	200 mg/day N=270 %	400 mg/day N=471 %	600 mg/day N=203 %
Ear and labyrinth disorders				
Vertigo	1	5	3	4
Tinnitus	1	0	2	2
Eye disorders				
Diplopia	2	6	10	16
Vision blurred	3	2	9	16
Conjunctivitis	<1	2	<1	0
Gastrointestinal disorders				
Nausea	4	7	11	17
Vomiting	3	6	9	16
Diarrhoea	3	3	5	4
Constipation	1	1	2	4
Flatulence	0	3	2	1
Dyspepsia	1	1	2	2
Toothache	1	2	2	1
Dry Mouth	1	1	1	2
Hypoaesthesia oral	0	0	1	1
General disorders and administration site conditions				
Fatigue	6	7	7	15
Gait disturbance	<1	<1	2	4
Asthenia	1	2	2	4
Irritability	1	1	2	2
Chest pain	1	2	1	2
Pyrexia	1	2	1	1
Feeling drunk	0	0	1	3
Oedema peripheral	0	1	<1	2
Feeling abnormal	<1	0	1	2

Table 1 Cont.: Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events ≥1% of Patients in the total VIMPAT group and More Frequent Than in the Placebo Group).

MedDRA System Organ Class/ Preferred Term	Placebo N=364 %	200 mg/day N=270 %	400 mg/day N=471 %	600 mg/day N=203 %
Infections and infestations				
Nasopharyngitis	6	6	8	4
Bronchitis	0	2	1	1
Rhinitis	<1	<1	1	1
Ear infection	<1	1	1	0
Cystitis	<1	1	<1	1
Gastroenteritis	0	1	<1	0
Injury, poisoning and procedural complications				
Contusion	3	3	4	2
Skin laceration	2	2	3	3
Fall	<1	1	2	1
Head injury	<1	2	1	1
Joint sprain	0	1	1	2
Investigations				
Positive rombergism	0	1	1	2
Gamma-glutamyltransferase increased	<1	2	<1	1
White blood cell count decreased	<1	0	<1	2
Metabolism and nutrition disorders				
Decreased appetite	<1	<1	2	3
Hypercholesterolaemia	<1	1	1	1
Musculoskeletal and connective tissue disorders				
Muscle spasms	<1	1	1	2
Neck pain	<1	1	1	1
Nervous system disorders				
Dizziness	8	16	30	53
Headache	9	11	14	12
Ataxia	2	4	7	15
Somnolence	5	5	8	8
Tremor	4	4	6	12
Nystagmus	4	2	5	10
Balance disorder	0	1	5	6
Memory Impairment	2	1	2	6
Cognitive disorder	<1	<1	2	2
Hypoaesthesia	1	2	2	2
Dysarthria	<1	<1	1	3
Disturbance in attention	1	0	1	2
Psychiatric disorders				
Depression	1	2	2	2
Insomnia	1	2	2	1
Confusional state	1	0	2	3
Mood altered	<1	1	1	2
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	<1	0	1	1
Epistaxis	0	1	1	0
Skin and subcutaneous tissue disorders				
Pruritus	1	3	2	3
Hyperhidrosis	<1	0	1	2

Table 2: Incidence of Most Common Dose-Related Treatment-Emergent Adverse Events in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events ≥1% of Patients in the total VIMPAT group and More Frequent Than in the Placebo Group).

MedDRA Preferred Term	Placebo N=364 %	200 mg/day N=270 %	400 mg/day N=471 %	600 mg/day N=203 %
Diplopia	2	6	10	16
Vision blurred	3	2	9	16
Nausea	4	7	11	17
Vomiting	3	6	9	16
Dizziness	8	16	30	53
Ataxia	2	4	7	15
Tremor	4	4	6	12
Nystagmus	4	2	5	10

Less Common Clinical Trial Adverse Drug Reactions (<1%): Other adverse events reorted by <1% of patients with partial-onset seizures in the total VIMPAT group in placebo-controlled clinical trials that occurred more frequently than in the placebo group were:

Eye disorders: eye irritation

Nervous system disorders: hypokinesia

Vascular disorders: hot flush

Cardiac Dose-dependent prolongations in PR interval with VIMPAT have been observed in clinical studies in patients and in healthy subjects (see **ACTION AND CLINICAL PHARMACOLOGY**). In clinical trials in patients with partial-onset seizures, asymptomatic first-degree AV block was observed as an adverse reaction in 0.4% (4/944) of patients randomized to receive VIMPAT and 0% (0/364) of patients randomized to receive placebo. In clinical trials in patients with diabetic neuropathy, asymptomatic first-degree AV block was observed as an adverse reaction in 0.6% (8/1393) of patients receiving VIMPAT and 0% (0/470) of patients receiving placebo. No second or higher degree AV block was seen in lacosamide treated epilepsy patients in controlled clinical trials. In clinical trials in patients with diabetic neuropathic pain, second-degree AV block has been rarely reported (<0.1%) (see **WARNINGS AND PRECAUTIONS**). However, cases with second and third degree AV block associated with lacosamide treatment have been reported in post-marketing experience (see **Post-Market Adverse Drug Reactions**). **Other Adverse Reactions in Patients with Partial-Onset Seizures** The following is a list of treatment-emergent adverse events reported by patients treated with VIMPAT in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials. Events addressed in other tables or sections are not listed here. Events included in this list from the controlled trials occurred more frequently on drug than on placebo and were based on consideration of VIMPAT pharmacology, frequency above that expected in the population, seriousness, and likelihood of a relationship to VIMPAT. Events are further classified within system organ class.

Blood and lymphatic system disorders: neutropenia, anemia

Cardiac disorders: palpitations

Nervous system disorders: paresthesia, cerebellar syndrome

Intravenous Adverse Reactions Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%). One case of profound bradycardia (26 bpm: BP 100/60 mmHg) was observed in a patient during a 15 minute infusion of 150 mg VIMPAT. This patient was on a beta-blocker. Infusion was discontinued and the patient recovered. ***Discontinuation Due to Adverse Events in Pre-marketing Controlled Clinical Studies*** In controlled clinical trials in patients with partial-onset seizures, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive VIMPAT at doses of 200 and 400 mg/day, respectively (placebo: 5%). At VIMPAT doses of 600 mg/day, 29% of the patients discontinued the trials due to adverse events. The adverse events most commonly (≥1% in the VIMPAT total group and greater than placebo) leading to discontinuation were dizziness, coordination abnormal, vomiting, diplopia, nausea, vertigo, and vision blurred. Other adverse events that led to discontinuation (<1% in the VIMPAT total group and greater than placebo) were typically CNS related and included tremor, nystagmus, fatigue, balance disorder, and disturbance in attention. **Comparison of Gender and Race:** The overall adverse event rate was similar in male and female patients. Although there were few non-Caucasian patients, no differences in the incidences of adverse events compared to Caucasian patients were observed. **Abnormal Hematologic and Clinical Chemistry Findings:** Abnormalities in liver function tests have been observed in controlled trials with VIMPAT in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥3x ULN (upper limit of normal) occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases >20x ULN was observed in one healthy subject 10 days after VIMPAT treatment completion, along with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without specific treatment. At the time of this event, bilirubin was normal. The hepatitis/nephritis was interpreted as a delayed hypersensitivity reaction to VIMPAT. **Drug Abuse and Dependence/Liability** Lacosamide showed no signs of abuse potential in three rat models. After prolonged administration to rats and dogs, there was no tolerance to lacosamide's pharmacological actions and abrupt cessation of treatment did not produce symptoms of psychological or physical dependence. In a human abuse potential study, single doses of 200 mg and 800 mg lacosamide produced euphoria-type subjective responses that differentiated

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

statistically from placebo; at 800 mg, these euphoria-type responses were statistically indistinguishable from those produced by alprazolam. The duration of the euphoria-type responses following lacosamide was less than that following alprazolam. A high rate of euphoria was also reported as an adverse event in the human abuse potential study following single doses of 800 mg lacosamide (15% [5/34]) compared to placebo (0%) and in two pharmacokinetic studies following single and multiple doses of 300-800 mg lacosamide (ranging from 6% [2/33] to 25% [3/12]) compared to placebo (0%). However, the rate of euphoria reported as an adverse event in the VIMPAT development program at therapeutic doses was less than 1%. Abrupt termination of lacosamide in clinical trials with diabetic neuropathic pain patients produced no signs or symptoms that are associated with a withdrawal syndrome indicative of physical dependence. However, psychological dependence cannot be excluded due to the ability of lacosamide to produce euphoria-type adverse events in humans.

Post-Market Adverse Drug Reactions Since the first global approval of VIMPAT on 29 August 2008 through 31 August 2011, there are approximately 123,654 patient-years of exposure to VIMPAT. In addition to the adverse events reported during clinical studies and listed above, the following adverse events have been reported in post-marketing experience. Table 3 is based on post-market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported to the company by the estimated number of patient years exposed to VIMPAT. Because these adverse events are reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Furthermore, a causal relationship between VIMPAT and the emergence of these events has not been clearly established.

Table 3: Post-Market Spontaneous Adverse Event Reports

Adverse events	Reported Frequency		
	Uncommon <1% and ≥0.1%	Rare <0.1% and ≥0.01%	Very Rare <0.01%
Immune system disorders			
Drug hypersensitivity reactions		X	
Multiorgan hypersensitivity reactions			X
Blood and lymphatic system disorders			
Leukopenia		X	
Thrombocytopenia		X	
Cardiovascular disorders			
Bradycardia		X	
Atrioventricular block		X	
Atrial fibrillation			X
Atrial flutter			X
Cardiac arrest			X
Cardiac failure			X
Myocardial infarction			X
Hepatobiliary disorders			
Liver function test abnormal		X	
Metabolism and nutrition disorders			
Hyponatremia		X	
Nervous system disorders			
Ataxia		X	
Syncope		X	
Psychiatric disorders			
Euphoric mood			X
Suicide attempt		X	
Suicide ideation		X	
Aggression		X	
Agitation		X	
Psychotic disorder		X	
Insomnia		X	
Hallucination		X	
Skin and subcutaneous skin disorders			
Rash	X		
Angioedema			X
Urticaria			X
Stevens-Johnson Syndrome			X

Cardiac disorders: Second and third degree AV block, and atrial fibrillation and atrial flutter associated with lacosamide treatment have been reported in post-marketing experience (see **WARNINGS AND PRECAUTIONS, Cardiac Rhythm and Conduction Abnormalities**).

DRUG INTERACTIONS VIMPAT (lacosamide) should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, pregabalin, beta- blockers) and in patients treated with class I antiarrhythmic drugs (see **WARNINGS AND PRECAUTIONS, Cardiac Rhythm and Conduction Abnormalities**). **In Vitro Assessment of Drug Interactions** *In vitro* metabolism studies indicate that lacosamide does not induce the enzyme activity of drug metabolizing cytochrome P450 isoforms CYP1A2, 2B6, 2C9, 2C19 and 3A4 at concentrations (12.5 µg/mL) close to the human peak plasma concentration (10.9µg/mL, C_{max}, steady state at maximum recommended human dose (MRHD) of 400 mg/day). At concentrations 10 times higher (125 µg/mL), enzyme activities were less than 2-fold increased. Lacosamide did not inhibit CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4/5 at concentrations up to 1000-fold greater than the C_{max} for 400 mg/day. The inhibitory concentrations (IC_{50}) of CYP3A4, 3A5, 2C9 and 1A1 by lacosamide are at least 70-fold higher than the C_{max} for 400 mg/day. *In vitro* data suggest that lacosamide has the potential to inhibit CYP2C19 at therapeutic concentrations (60% inhibition at 25 µg/mL). However, an *in vivo* evaluation in healthy subjects showed no inhibitory effect of lacosamide (600 mg/day administered as 300 mg BID dosing) on the single dose pharmacokinetics of omeprazole (40 mg). Lacosamide is a CYP2C19 substrate. The relative contribution of other CYP isoforms or non-CYP enzymes in the metabolism of lacosamide is not clear. Lacosamide was not a substrate or inhibitor for P-glycoprotein. Since <15% of lacosamide is bound to plasma proteins, a clinically relevant interaction with other drugs through competition for protein binding sites is unlikely. **In Vivo Assessment of Drug Interactions** Drug-drug interaction studies in healthy subjects showed no pharmacokinetic interactions between VIMPAT and carbamazepine, valproic acid, digoxin, metformin, omeprazole, midazolam, or an oral contraceptive containing ethinylestradiol and levonorgestrel. There was no evidence for any relevant drug-drug interaction of VIMPAT with common AEDs in the placebo-controlled clinical trials in patients with partial-onset seizures. The lack of pharmacokinetic interaction does not rule out the possibility of pharmacodynamic interactions, particularly among drugs that affect the heart conduction system. **Drug – Drug Interactions Drug- Interaction Studieswith AEDs:** *Effect of VIMPAT on concomitant AEDs:* VIMPAT 400 mg/day had no influence on the pharmacokinetics of 600 mg/day valproic acid and 400 mg/day carbamazepine in healthy subjects. The placebo-controlled clinical studies in patients with partial-onset seizures showed that steady-state plasma concentrations of levetiracetam, carbamazepine, carbamazepine epoxide, lamotrigine, topiramate, oxcarbazepine monohydroxy derivative (MHD), phenytoin, valproic acid, phenobarbital, gabapentin, clonazepam, and zonisamide were not affected by concomitant intake of VIMPAT at 200 to 600 mg/day. *Effect of concomitant AEDs on VIMPAT:* Drug-drug interaction studies in healthy subjects showed that 600 mg/day valproic acid had no influence on the pharmacokinetics of 400 mg/day VIMPAT. Likewise, 400 mg/day carbamazepine had no influence on the pharmacokinetics of VIMPAT (400 mg/day) in a healthy subject study. Population pharmacokinetics results in patients with partial-onset seizures showed small reductions (approximately 25% lower) in lacosamide plasma concentrations when VIMPAT (200 to 600 mg/day) was coadministered with carbamazepine, phenobarbital or phenytoin. **Drug-Drug Interaction Studies with Other Drugs: Digoxin** VIMPAT (400 mg/day) did not affect pharmacokinetics of digoxin (0.5 mg once daily) in a study in healthy subjects. There was no effect of digoxin on the pharmacokinetics of VIMPAT. **Metformin** There were no clinically relevant changes in metformin levels following co-administration of VIMPAT (400 mg/day). Metformin (500 mg three times a day) had no effect on the pharmacokinetics of VIMPAT (400 mg/day) in healthy subjects. **Omeprazole** Omeprazole is a CYP2C19 substrate and inhibitor. Omeprazole (40 mg once daily) increased the AUC of lacosamide by 19% (300 mg, single dose), which is unlikely to be clinically significant. Lacosamide (600 mg/day) did not affect the single-dose pharmacokinetics of omeprazole (40 mg) in healthy subjects. **Midazolam** Midazolam is a 3A4 substrate. VIMPAT administered as a single 200 mg dose or repeated doses of 400 mg/day (200 mg BID) to healthy subjects had no clinically relevant effect on the AUC of midazolam, but slightly increased the C_{max} over time (30% after 13 days). **Oral Contraceptives** In an interaction trial in healthy subjects, there was no clinically relevant interaction between lacosamide (400 mg/day) and the oral contraceptives ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg). Progesterone concentrations were not affected when the medicinal products were co-administered (see **WARNINGS AND PRECAUTIONS, Women of Childbearing Potential/Contraception**). **Drug-Food Interactions** VIMPAT is completely absorbed after oral administration. Food does not affect the rate or extent of absorption. **Drug-Herb Interactions** Interactions with herbal products have not been evaluated. **Drug-Laboratory Interactions** Interactions with laboratory tests have not been observed. **REPORTING SUSPECTED SIDE EFFECTS** You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Administration

DOSAGE AND ADMINISTRATION

General Considerations VIMPAT (lacosamide) may be taken with or without food. **Film-coated tablets** On the first day of treatment the patient starts with VIMPAT 50 mg tablets twice a day. During the second week, the patient takes VIMPAT 100 mg tablets twice a day. Depending on response and tolerability, VIMPAT 150 mg tablets may be taken twice a day during the third week and VIMPAT 200 mg tablets twice a day during the fourth week. **Solution for injection** The solution for injection is infused over a period of 30 to 60 minutes twice daily. VIMPAT solution for injection can be administered intravenously (IV) without further dilution. Conversion to or from oral and IV administration can be done directly without titration. The total daily dose and twice daily administration should be maintained. There is experience with twice daily infusions of VIMPAT up to 5 days (n=53). **Compatibility and Stability** VIMPAT solution for injection can be administered intravenously without further dilution or may be mixed with diluents. VIMPAT solution for injection was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in glass or polyvinyl chloride (PVC) bags at room temperature (15-30°C).

Diluents:

Sodium Chloride Injection 0.9% (w/v)

Dextrose Injection 5% (w/v)

Lactated Ringer's Injection

The stability of VIMPAT solution for injection in other infusion solutions has not been evaluated. Product with particulate matter or discoloration should not be used. Any unused portion of VIMPAT solution for injection should be discarded. Do not use if solution shows haziness, particulate matter, discoloration or leakage. **Recommended Dose and Dosage Adjustment Adults** The recommended starting dose for VIMPAT is 50 mg twice a day, with or without food, 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 can be further increased by 50 mg twice a day every week, to a maximum recommended daily dose of 400 mg (200 mg twice a day). Doses above 400 mg/day do not confer additional benefit, are associated with more severe and substantially higher frequency of adverse reactions and are not recommended. In accordance with current clinical practice, if VIMPAT has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). VIMPAT therapy can be initiated with either oral or intravenous (IV) administration. **Patients with Renal Impairment** No dose adjustment is necessary in patients with mild or moderate renal impairment (creatinine clearance [CL_{CR}] >30 mL/min). A maximum dose of 300 mg/day is recommended for patients with severe renal impairment (CL_{CR} ≤30 mL/min) and in patients with end-stage renal disease. In all patients with any degree of renal impairment, the dose titration should be performed with caution (see **ACTION AND CLINICAL PHARMACOLOGY, Special**

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

Populations and Conditions, Renal Impairment). Following a 4-hour hemodialysis treatment, AUC of VIMPAT was reduced by approximately 50%. Thus, dosage supplementation of up to 50% following hemodialysis may be considered. Treatment of patients with end-stage renal disease should be made with caution as there is limited clinical experience in subjects (n=8) and no experience in patients, and there is accumulation of a metabolite (with no known pharmacological activity). **Patients with Hepatic Impairment** The dose titration should be performed with caution in patients with mild to moderate hepatic impairment. A maximum dose of 300 mg/day is recommended for patients with mild or moderate hepatic impairment. The pharmacokinetics of VIMPAT have not been evaluated in severe hepatic impairment. VIMPAT is not recommended in patients with severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**).

Geriatrics (≥65 years of age) Clinical experience with VIMPAT in elderly patients with epilepsy is limited (n=18). Although no dose reduction is necessary in elderly patients, caution should be exercised during dose titration and age-associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**). **Pediatrics (<18 years of age)** The safety and effectiveness of VIMPAT in pediatric patients <18 years has not been established, and therefore its use in this patient population is not indicated (see **INDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**). **Missed Dose** If the patient misses a dose by a few hours, they should be instructed to take VIMPAT as soon as they remember. If it is close to their next dose, they should be instructed to take their medication at the next regular time. Patients should not take two doses at the same time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans There is limited clinical experience with VIMPAT (lacosamide) overdose in humans. Clinical symptoms (dizziness and nausea) following doses of 1200 mg/day were mainly related to the central nervous system and the gastrointestinal system. There has been a single case of intentional overdose by a patient who self-administered 12 grams VIMPAT along with large doses of zonisamide, topiramate, and gabapentin. The patient presented in a coma and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later. During pre-marketing controlled clinical studies, no intentional overdose of VIMPAT resulted in death.

Treatment or Management of Overdose There is no specific antidote for overdose with VIMPAT. Standard decontamination procedures should be followed. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Poison Control Centre should be contacted for up to date information on the management of overdose with VIMPAT. Standard hemodialysis procedures result in significant clearance of VIMPAT (reduction of systemic exposure by 50% in 4 hours). Hemodialysis has not been performed in the few known cases of overdose, but may be helpful based on the patient's clinical state or in patients with significant renal impairment.

SUPPLEMENTAL PRODUCT INFORMATION

STORAGE AND STABILITY

Store at room temperature (15 – 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

VIMPAT (lacosamide) tablets

VIMPAT film-coated tablets are supplied as follows:

50 mg tablet: VIMPAT tablets 50 mg lacosamide are pink, oval, film-coated tablets debossed with "SP" on one side and "50" on the other. They are supplied in high density polyethylene (HDPE) bottles of 60 tablets.

100 mg tablet: VIMPAT tablets 100 mg lacosamide are dark yellow, oval, film-coated tablets debossed with "SP" on one side and "100" on the other. They are supplied in HDPE bottles of 60 tablets.

150 mg tablet: VIMPAT tablets 150 mg lacosamide are salmon, oval, film-coated tablets debossed with "SP" on one side and "150" on the other. They are supplied in HDPE bottles of 60 tablets.

200 mg tablet: VIMPAT tablets 200 mg lacosamide are blue, oval, film-coated tablets debossed with "SP" on one side and "200" on the other. They are supplied in HDPE bottles of 60 tablets.

VIMPAT tablets contain the following nonmedicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and dye pigments as specified below:

VIMPAT tablets are supplied as debossed tablets and contain the following coloring agents:
50 mg tablets: red iron oxide, black iron oxide, FD&C Blue #2/indigo carmine aluminum lake
100 mg tablets: yellow iron oxide
150 mg tablets: yellow iron oxide, red iron oxide, black iron oxide
200 mg tablets: FD&C Blue #2/indigo carmine aluminum lake

VIMPAT solution for injection

VIMPAT solution for injection is a clear, colorless, sterile solution containing 20 mL of 10 mg lacosamide per mL for intravenous infusion. The nonmedicinal ingredients are sodium chloride and water for injection. Hydrochloric acid is used for pH adjustment. VIMPAT solution for injection has a pH of 3.8 to 5.0.

VIMPAT solution for injection 10 mg/mL is supplied in 20 mL colorless single-use glass vials, 10 mg/mL vial.

Product Monograph available on request.

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Date of preparation: June 2012

UCB Canada Inc.
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PAAB

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William Dennis Chair in Epilepsy Research

The Faculty of Medicine at Dalhousie University is pleased to invite applications for the William Dennis Chair in Epilepsy Research. The Chairholder will develop and direct an internationally recognized research program in epilepsy, emphasizing the potential for translation and application to clinical practice. Of equal importance is the ability of the Chair to interact with the broad community both to educate and to increase public awareness and understanding of epilepsy. The Chair will become a leader in efforts to understand the causes, prevention, diagnosis and treatment of epilepsy.

This is an outstanding opportunity for a researcher with PhD and/or MD qualifications in research areas including but not restricted to basic science, genetics, epidemiology, outcomes or the behavioral sciences to build a program with strong clinical ties. We wish to attract a talented and energetic leader with an established record in epilepsy research, preferably in Pediatrics. A demonstrated ability to attract external funding and support and to sustain a strong research program is essential. Candidates must be inclusive and collaborative in leadership style and knowledge sharing, and interested in shaping a strategy for epilepsy research, clinical practices and community outreach in the region and beyond.

The successful candidate will receive academic rank and cross appointments commensurate with qualifications and experience. For clinician scientist applicants, the candidate must hold, or be eligible for, a license with the appropriate licensing authority.

Halifax, located on the seacoast of Nova Scotia, and the largest city in Atlantic Canada, boasts a rich diversity of recreational, cultural and educational opportunities.

Application period will close October 1 or until the position is filled. Please send a curriculum vitae, a two-page description of your proposed research program, a brief statement of teaching philosophy, and arrange to have 3 letters of reference (2 of which must be academic) sent under separate cover directly to Dr. Gerry Johnston, Chair of Search & Selection Committee c/o Jesslyn Kinney, Program Manager, Medical Research Development Office, Dalhousie University, 5849 University Avenue, Room C203, PO Box 15000, Halifax, NS Canada B3H 4R2. E-mail: mrdo@dal.ca

All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. Dalhousie University is an Employment Equity/Affirmative Action employer. The University encourages applications from qualified Aboriginal people, persons with a disability, racially visible persons and women.

Discovery and Innovation for Health

See our AD on A-8, A-9

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https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

P COPAXONE®
(glatiramer acetate injection)

Treat from the start. Treat for the long run.

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Immunomodulator

INDICATIONS AND CLINICAL USE

COPAXONE® is indicated for: the treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS), to decrease the frequency of clinical exacerbations, to reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans; for the treatment of patients who have experienced a single demyelinating event, accompanied by abnormal MRI scans and are considered to be at risk of developing Clinically Definite MS (CDMS), after alternative diagnoses are excluded, to delay the onset of definite MS, to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans).

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.

CONTRAINDICATIONS

COPAXONE® (glatiramer acetate) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

Safety Information

WARNINGS AND PRECAUTIONS

The only recommended route of administration of COPAXONE® (glatiramer acetate) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Cardiovascular; *Symptoms of Potentially Cardiac Origin:* Approximately 13% of COPAXONE® patients in the multicenter controlled trials (compared to 5% of placebo patients) experienced at least one episode of what was described as transient chest pain (see ADVERSE REACTIONS: Chest Pain). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see ADVERSE REACTIONS: Immediate Post-Injection Reaction), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see ADVERSE REACTIONS: Immediate Post-Injection Reaction).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

General: Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate), including a careful review of the Part III – Consumer Information. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Localized Adverse Reactions Associated with Subcutaneous Use: At injection sites, localized lipoatrophy and, rarely, injection-site skin necrosis have been reported during clinical trials and post-marketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis (see Part III – Consumer Information).

Immune: ***Considerations Involving the Use of a Product Capable of Modifying Immune Responses:*** **COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.**

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RRMS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested. Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

Carcinogenesis and Mutagenesis: Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see TOXICOLOGY: Carcinogenicity). The relevance of these findings for humans is unknown (see PRECAUTIONS – Considerations Involving the Use of a Product Capable of Modifying Immune Responses).

Renal: The pharmacokinetics of COPAXONE® in patients with impaired renal function have not been determined.

Special Populations: Pregnant Women: There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies (see TOXICOLOGY: Reproduction and Teratology). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre-marketing clinical trials with COPAXONE®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE® should only be considered after careful risk/benefit assessment and be used with caution.

Pediatrics (< 18 years of age): The safety and effectiveness of COPAXONE® have not been established in individuals below 18 years of age.

Geriatrics (> 65 years of age): COPAXONE® has not been studied in the elderly (> 65 years old).

Monitoring and Laboratory Tests: Data collected pre- and post-market do not suggest the need for routine laboratory monitoring.

ADVERSE REACTIONS

Adverse Drug Reaction Overview: In the 4 placebo-controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® occurring at an incidence of at least 10% and at least 1.5 times higher than in placebo-treated patients were: injection-site reactions, vasodilatation, rash, dyspnea and chest pain.

In the placebo-controlled clinical trials approximately 5% discontinued treatment due to an adverse event compared to 1% for placebo-treated patients. The adverse events most commonly associated with discontinuation were (in order of descending frequency): injection-site reactions, dyspnea, urticaria, vasodilatation and hypersensitivity. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life-threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 14% of Multiple Sclerosis patients exposed to COPAXONE® in the 4 placebo-controlled studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE® compared to 2% for placebo-treated patients. An immediate post-injection reaction is a constellation of symptoms occurring immediately after injection that includes at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (individual symptoms are listed separately in Table 1). These symptoms were invariably transient, self-limited, did not require specific *treatment and in general, arose several months after initiation of treatment, although they may occur earlier* in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see WARNINGS AND PRECAUTIONS: Symptoms of Potentially Cardiac Origin).

Chest Pain: Approximately 13% of glatiramer acetate patients in the 4 placebo-controlled studies (compared to 5% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment *for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown* (see WARNINGS AND PRECAUTIONS: Symptoms of Potentially Cardiac Origin). For adverse event reporting, please contact Health Canada by phone at: 1-866-234-2345, or Teva Canada Innovation at: 1-800-283-0034.

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

ADMINISTRATION

DOSAGE AND ADMINISTRATION

COPAXONE® *should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.* The only recommended route of administration of COPAXONE® (glatiramer acetate) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Recommended Dose and Dosage Adjustment: The recommended dose of COPAXONE® (glatiramer acetate injection) for the treatment of Clinically Isolated Syndrome and Relapsing Remitting MS is a daily injection of 20 mg given subcutaneously. Please see the Part III – Consumer Information – pre-filled syringe for instructions on the preparation and injection of COPAXONE®.

Missed Dose: If a dose is missed it should be taken as soon as possible. If, however, it is closer to the time of the next dose, skip the missed dose and resume at the usual dosing schedule.

Avoid giving 2 injections in the same 12-hour period.

SUPPLEMENTAL PRODUCT INFORMATION

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions: *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.* The adverse reaction data in this section is derived from 4 pivotal, double-blind, placebo-controlled clinical trials which were conducted during pre-marketing and post-marketing periods in a total of 512 patients treated with glatiramer acetate and 509 patients treated with placebo for up to 36 months. Three trials were conducted in RRMS. The fourth trial was in patients presenting with a first clinical event and MRI features suggestive of MS and included 243 patients treated with glatiramer acetate and 238 patients treated with placebo. All adverse events were recorded by the clinical investigators, using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into standardized categories using MedDRA dictionary terminology. The following table lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with glatiramer acetate in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo.

Table 1: Controlled Trials – Incidence of Glatiramer Acetate Adverse Reactions ≥2% and More Frequent than Placebo

MedDRA Version 10.0		GA 20 mg (n=512) % of Patients	Placebo (n=509) % of Patients
Blood and Lymphatic System Disorders	Lymphadenopathy	7.2	2.9
Cardiac Disorders	Palpitations	7.6	3.3
	Tachycardia	4.7	1.6
Eye Disorders	Eye Disorder	3.3	1.2
	Diplopia	2.9	1.8
Gastrointestinal Disorders	Nausea	14.5	10.4
	Vomiting	7.4	4.3
	Constipation	7.0	6.3
	Dyspepsia	6.6	6.5
	Dysphagia	2.3	1.2
	Fecal Incontinence	2.3	2.0
General Disorders and Administration Site Conditions	Injection-Site Erythema	46.1	10.6
	Injection-Site Pain	36.3	17.1
	Injection-Site Mass	25.8	5.9
	Injection-Site Pruritus	24.4	2.8
	Asthenia	23.8	23.2
	Injection-Site Edema	20.9	4.5
	Pain	18.9	16.7
	Chest pain	12.5	4.9
	Injection-Site Inflammation	8.2	1.6
	Injection-Site Reaction	8.2	1.4
	Pyrexia	6.4	5.7
	Injection-Site Hypersensitivity	4.1	0.0
	Local Reaction	3.7	1.4
	Face Edema	3.3	0.6
	Edema Peripheral	3.3	2.4
	Chills	2.9	0.4
	Injection-Site Atrophy*	2.0	0.0
	Injection-Site Fibrosis	2.0	0.6
Immune System Disorders	Hypersensitivity	3.3	1.8
Infections and Infestations	Infection	31.8	30.8
	Influenza	15.4	14.5
	Rhinitis	7.4	5.9
	Bronchitis	6.4	5.7
	Gastroenteritis	6.3	4.3
	Vaginal Candidiasis	4.9	2.6
	Otitis Media	3.7	2.9
	Herpes Simplex	2.5	1.8
	Tooth Abscess	2.3	2.2
Metabolism and Nutrition Disorders	Weight Increased	2.9	0.8
	Anorexia	2.3	2.2
Musculoskeletal and Connective Tissue Disorders	Back Pain	13.5	11.2
	Arthralgia	10.4	9.4
	Neck Pain	4.5	3.9
Nervous System Disorders	Headache	30.9	29.1
	Hypertonia	7.8	7.3
	Tremor	4.1	1.8
	Migraine	3.7	2.4
	Syncope	3.1	1.8
Psychiatric Disorders	Depression	13.1	12.0
	Anxiety	11.1	8.8
	Nervousness	2.3	1.0
Renal and Urinary Disorders	Micturition Urgency	5.1	4.3
	Pollakiuria	4.7	4.5
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	13.3	2.8
	Cough	6.6	5.3
Skin and Subcutaneous Tissue Disorders	Rash	13.7	9.0
	Hyperhidrosis	6.6	4.7
	Pruritus	5.1	4.3
	Ecchymosis	3.5	3.3
	Urticaria	3.1	1.6
	Skin Disorder	2.9	0.8
Vascular Disorders	Vasodilatation	18.0	4.7

* "Injection-site atrophy" comprises terms relating to localized lipoatrophy at injection site.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender-related differences. No clinically significant differences were identified. In these clinical trials 96% of patients were Caucasian. This percentage reflects the higher representation of Caucasian in the MS population, even though it does not reflect the exact world racial distribution among MS patients. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups. Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any placebo-controlled trial due to abnormal laboratory findings which were assessed as possibly related to glatiramer acetate.

Other Adverse Events Observed During All Clinical Trials: In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), with a subset of patients continuing to 10 years (n=108) and some patients to an average of 13.6 years (n=100) in open-label extensions at a daily dose of 20 mg. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using *COSTART II* dictionary terminology. *All reported events that occurred at least twice and* potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients. **Body as a whole:** *Frequent:* Injection-site edema, injection-site atrophy, abscess and injection-site hypersensitivity. *Infrequent:* Injection-site hematoma, injection-site fibrosis, moon face, cellulitis, generalized edema, hernia, injection-site abscess, serum sickness, suicide attempt, injection-site hypertrophy, injection-site melanosis, lipoma, and photosensitivity reaction. **Cardiovascular:** *Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins. **Digestive:** *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration and duodenal ulcer. **Endocrine:** *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. **Gastrointestinal:** *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. **Hemic and Lymphatic:** *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. **Metabolic and Nutritional:** *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. **Musculoskeletal:** *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. **Nervous:** *Frequent:* Abnormal dreams, emotional lability and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. **Respiratory:** *Frequent:* Hyperventilation, hay fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. **Skin and Appendages:** *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. **Special Senses:** *Frequent:* Visual field defect. *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. **Urogenital:** *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Post-Marketing Adverse Drug Reactions

Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials: Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate) in either ongoing phases of clinical trials or from spontaneous reports, that have been received since market introduction and that may have or not have causal relationship to the drug include the following: **Body as a Whole:** Sepsis, SLE syndrome, hydrocephalus, enlarged abdomen, injection-site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. **Cardiovascular:** Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy, cardiomegaly, arrhythmia, angina pectoris, tachycardia. **Digestive:** Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. **Hemic and Lymphatic:** Thrombocytopenia, lymphoma-like reaction, acute leukemia. **Metabolic and Nutritional:** Hypercholesteremia. **Musculoskeletal:** Rheumatoid arthritis, generalized spasm. **Nervous:** Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. **Respiratory:** Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. **Skin and Appendages:** Herpes simplex, pruritis, rash, urticaria. **Special Senses:** Glaucoma, blindness, visual field defect. **Urogenital:** Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency. **Localized Adverse Reactions Associated with Subcutaneous Use:** At injection sites, localized lipoatrophy and, rarely, injection-site skin necrosis have been reported during post-marketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis (see Part III – Consumer Information).

DRUG INTERACTIONS

Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial did not report any serious or unexpected adverse events thought to be related to treatment.

OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. *Neither patient evidenced any change in blood pressure, heart rate, or temperature.* Telephone follow-up *several hours later produced no report of* adverse experiences from either patient. The maximum COPAXONE® dose reported in an overdose case is 80 mg glatiramer acetate injection.

For management of a suspected overdose, contact your Regional Poison Centre.

Based on Product Monograph dated July 7, 2011. Product Monograph available on request.

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See our AD on A-3

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press

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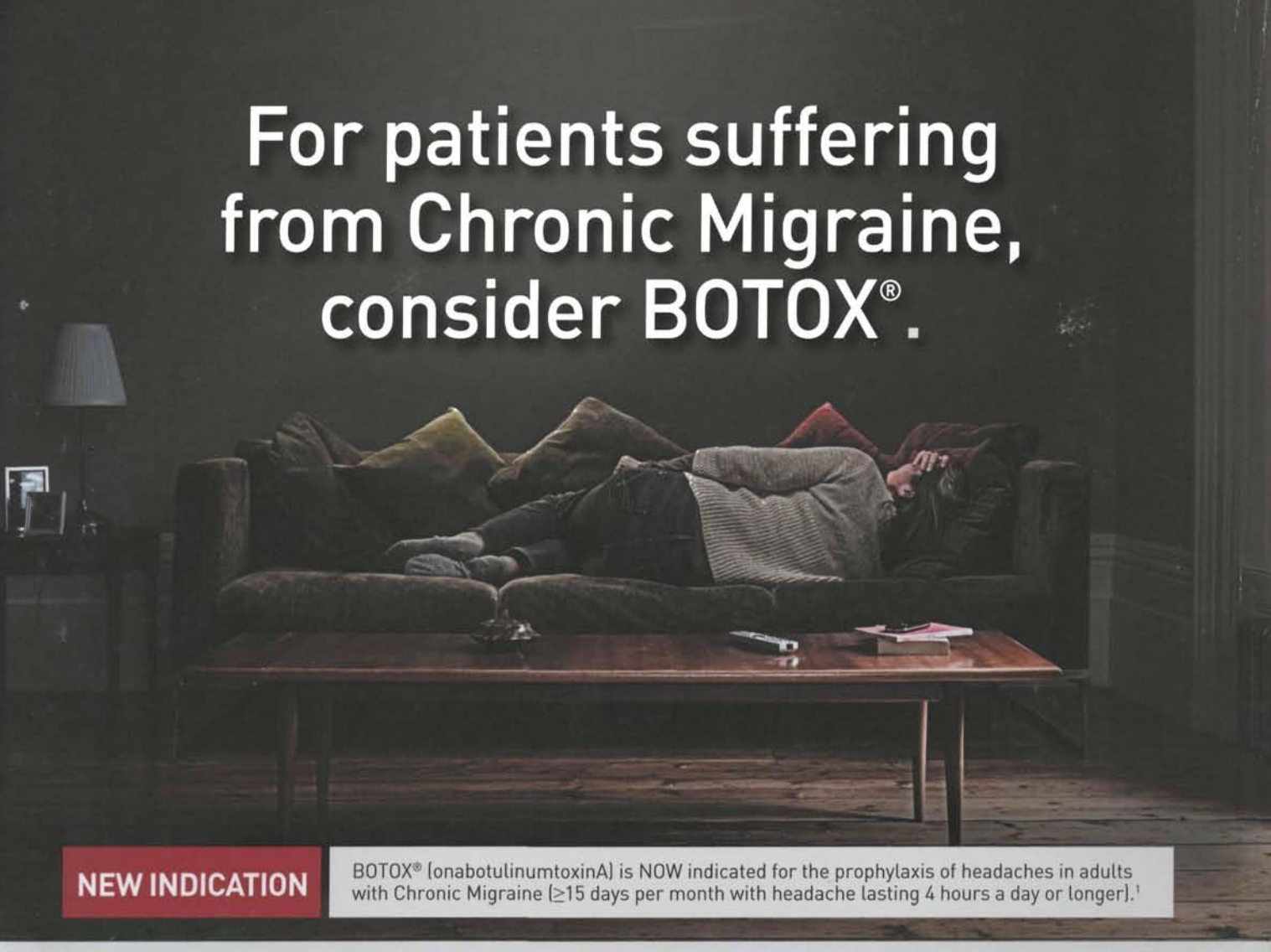
For patients suffering from Chronic Migraine, consider BOTOX®.



NEW INDICATION

BOTOX® (onabotulinumtoxinA) is NOW indicated for the prophylaxis of headaches in adults with Chronic Migraine (≥15 days per month with headache lasting 4 hours a day or longer).[1]

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

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BOTOX® onabotulinumtoxinA

see prescribing information pn pages A-17 to 19

https://doi.org/10.1017/S0317167100118670 Published online by Cambridge University Press