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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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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 pregabalin 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.

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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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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.

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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.

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 on 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 studies.

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

ALLERGAN BOTOX® onabotulinumtoxinA PAAB

See our AD on A-3

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CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

Congress Agenda as of Dec. 5, 2011

2012 Canadian Neurological Sciences Federation Annual Congress, June 6-8, 2012

Pre-Congress SIGs evening of June 5 *Special Interest Groups*

Tuesday, June 5/12

18:00 - 20:00	**Movement Disorders SIG** *David Grimes*
18:00 - 20:00	**Headache SIG** *Suzanne Christie*
18:00 - 20:00	**Epilepsy Video SIG** *Seyed Mirsattari*
18:00 - 20:00	**Neuromuscular Diseases SIG** *Mike Nicolle*

Wednesday, June 6/12

07:00 - 08:45	**Delegate Continental Breakfast**
09:00 - 16:45	**Neurology Resident Review – Neuromuscular Diseases** *Kristine Chapman, Laine Greene*
09:00 - 16:45	**Neurosurgery Resident Review – Neuro-oncology** *David Eisenstat, Joe Megyesi, Roberto Diaz*
09:00 - 16:45	**ALS Day**
09:00 - 12:00	**Hydrocephalus** *Mark Hamilton*
09:00 - 12:00	**Stroke** *Dariush Dowlatshahi*
09:00 - 12:00	**Hot Topics in Child Neurology** *Asif Doja*
12:00 - 13:45	**Lunch & Poster Viewing**
12:15 - 13:30	**Co-developed Industry Symposium (Stroke)**
12:15 - 13:30	**Co-developed Industry Symposium (Topic TBA)**
13:45 - 16:45	**Dementia** *Andrew Frank*
13:45 - 16:45	**Headache** *Jonathan Gladstone*
13:45 - 16:45	**Neurocritical Care** *Draga Jichici, Jeanne Teitelbaum*
16:45 – 19:30	**Exhibitors Reception**

Thursday, June 7/12

07:00 - 08:15	**Delegate Continental Breakfast**
08:30 - 10:45	**Grand Plenary – Gloor Lecture:** *Lawrence Hirsch,* **Tibbles Lecture:** *Marjo van der Knaap,* **Penfield Lecture:** *TBA,* **Richardson Lecture:** *TBA*
11:00 - 17:00	**Child Neurology Day** *Michelle Demos, Cecil Hahn*
11:00 - 12:30	**CNS / CSCN Chair's Select Abstracts**
11:00 - 12:30	**CNSS Chair's Select Abstracts**
12:30 - 14:15	**Lunch, Exhibit & Poster Viewing**
12:45 - 14:00	**Co-developed Industry Symposium (Epilepsy)**
12:45 - 14:00	**Co-developed Industry Symposium (Neuropathic Pain)**
14:15 - 17:15	**Multiple Sclerosis** *Mark Freedman*
14:15 - 17:15	**EEG** *Seyed Mirsattari*
14:15 - 17:15	**Neurosurgical Education and Workforce in Canada** *Chris Wallace*
14:15 - 17:15	**Evidence Based Neurosurgery** *Brian Toyota*
17:30 – 19:00	**Poster Author Stand-by Tour #1**

Friday, June 8/12

07:00 - 07:45	**Delegate Continental Breakfast**
08:00 - 11:00	**Platform Sessions**
11:15 - 13:00	**Grand Rounds**
13:15 - 14:45	**Lunch, Exhibition & Poster Author Stand-by Tour #2**
14:45 - 17:45	**Epilepsy** *Sharon Whiting*
14:45 - 17:45	**Neurogenetics** *Matthew Farrer*
14:45 - 17:45	**Neuro-ophthalmology** *Jason Barton*
14:45 - 17:45	**Spine** *Eric Massicotte*
14:45 - 17:45	**Neurovascular & Interventional Neuroradiology** *Gary Redekop*

Jacob wears a lot of labels these days

"Fictitious patient. May not be representative of all patients".

None of them quite stick

Life has not been easy for Jacob. He was referred to a psychiatrist by the hospital following an acute psychotic episode, but as a clumsy boy with learning difficulties he had a history of many other labels, none of which quite seemed to stick. In his late teens Jacob's behaviour became more troubling. He was treated medically for depression and received counselling – it didn't seem to help much.

Jacob was initially diagnosed with schizophrenia, but his psychiatrist was concerned about his awkward gait, and he didn't respond well to antipsychotics. After trying to further understand the pattern of Jacob's labels, the psychiatrist referred him to a metabolic specialist.

That's how we know now that it was Niemann-Pick type C disorder hiding behind those labels.

Luckily Jacob was diagnosed before his neurological symptoms became incapacitating, and management options were available.

Do you have patients with an atypical history of psychotic symptoms and labels that don't quite stick? If you suspect the possibility that a patient has an underlying metabolic condition such as Niemann-Pick type C, you should refer them to a neurologist, neuropsychiatrist or metabolic specialist. Management options are available for certain neurodegenerative disorders, and specialized metabolic centres may help initiate and follow up this treatment.

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