BOTOX
onabotulinumtoxinA
INJECTION

The only clinically proven preventative treatment for adults with Chronic Migraine*

www.botox-migraine.ca

WARNING: DISTANT SPREAD OF TOXIN EFFECT
Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms.

**patients with Chronic Migraine experience 12 fewer headache days per month compared to baseline (vs. 10 days with placebo) at 24 weeks[1]*

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Chronic Migraine is different.

- The World Health Organization (WHO) ranks migraine as one of the top 20 most disabling diseases[2]

- Chronic Migraine is a severe neurological disorder that is distinct from Episodic Migraine[2].

- Patients with *Chronic Migraine* suffer from headaches 15 days or more per month, lasting four hours a day or longer, of which 8 of those days meet the criteria for migraine[2]. Patients with *Episodic Migraine* experience migraine pain that is less frequent and varies in duration[2].

- Based on global estimates, over 270,000 Canadians who are 18 years of age and older are Chronic Migraine sufferers[3].

- Population-based studies have shown that those with Chronic Migraine demonstrate higher individual and societal burden because they are more disabled than those with Episodic Migraine and have an impaired quality of life[4].

- It is estimated that approximately 80% of those who meet the definition of Chronic Migraine have not received an accurate diagnosis[5] and may be unaware of their treatment options.

- Until now, treatments for adults with Chronic Migraine have been limited to therapies that treat migraine pain once it has started. **Botox®** is the only clinically-studied and approved preventative treatment for adult patients with Chronic Migraine in Canada[1,6].

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Prevent Chronic Migraine pain before it starts.

Does your patient suffer from Chronic Migraine?

Are current treatments failing to provide adequate relief?

Is your patient using more acute medications than recommended?

If the answer is *YES*, consider Botox® (onabotulinumtoxinA) – a treatment that prevents migraine pain before it starts.

Botox® is indicated for the prophylaxis of headaches in adult patients (18 years of age or older) with Chronic Migraine (≥15 days per month with headache lasting 4 hours a day or longer)[6].

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies[6].

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Clinically proven migraine prophylaxis in adults with Chronic Migraine[1].

PREEMPT - A randomized, placebo-controlled double-blind study to evaluate Botox® efficacy in adults[1]

- PREEMPT = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy
- Subjects were randomized to receive placebo or **Botox®** injections at 12 and 24 weeks

Key elements of study design:

Patient population	N = 699
Headache days during 28-day baseline period	≥ 15 lasting 4 hours or more (≥ 50% being migraine/probable migraine)
Concurrent headache prophylaxis	None
Acute headache treatments	Allowed

Compared to placebo, patients treated with Botox® had:

- ✓ **Fewer headache days per month from Week 4 to Week 24[1]**
- ✓ **Fewer cumulative hours of headache on headache days by Week 24[1]**

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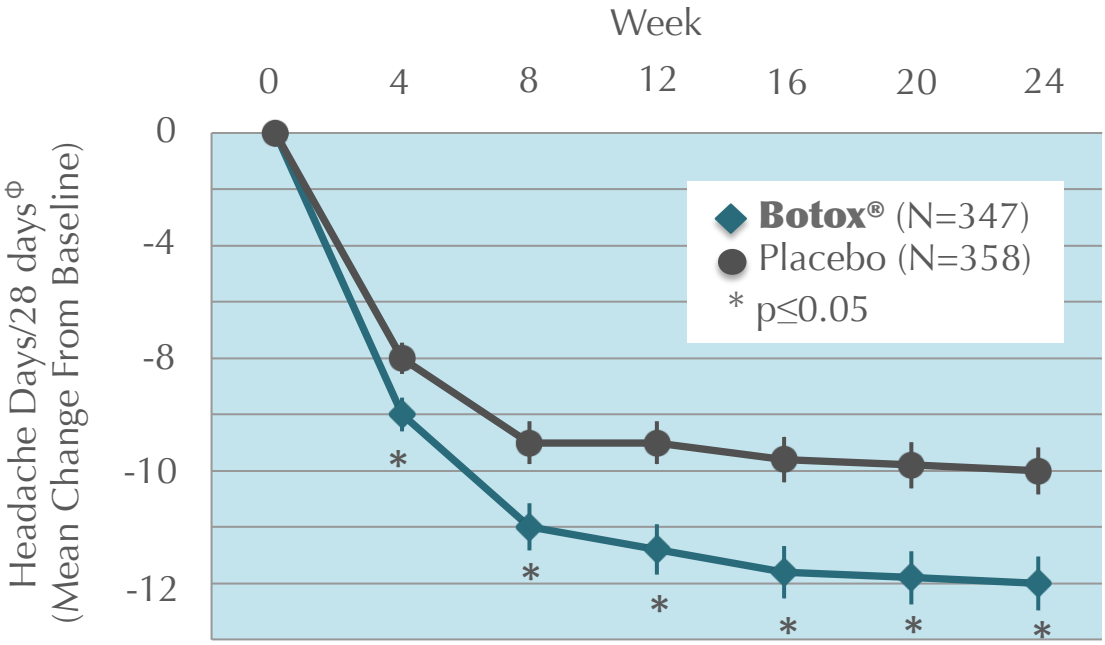
Statistically significant, clinically meaningful

Week 24 Key Efficacy Variables[1]

Efficacy per 28 days[Φ]	Botox® (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-12.2*	-10.0
Change from baseline in total cumulative hours of headache on headache days	-134*	-95

* Significantly different from placebo ($p \leq 0.05$)

Mean Change from Baseline in Number of Headache Days[1]



[Φ] A headache day was defined as a calendar day per 28 days with ≥ 4 continuous hours of headache[1]

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A dosing and administration protocol that works[6].

In-Office Administration

- **Botox**® should be administered in an office setting by a qualified medical specialist, such as a neurologist, headache or pain specialist[6].

Established Treatment Protocol

- Patients should be given at least 2 **Botox**® treatments, 12 weeks apart[1,6], to determine effectiveness.
- Further re-treatment should be determined per clinician's discretion.

Lasting results

- When injected at labeled doses and at the recommended locations, **Botox**® is expected to produce results lasting up to three months (12 weeks) depending on the individual patient[1,6].

Proven Dose

- *Recommended injection sites*: patients are given injections at 31-39 sites across seven specific head and neck muscles to prevent onset of headaches[1,6].
- *Recommended dose*: 155 Units administered intramuscularly using a sterile 30-guage, 0.5 inch needle as 0.1 mL (5 Units) injections per site[1,6].

For complete dosing and administration information for Botox®, consult full prescribing information[6].

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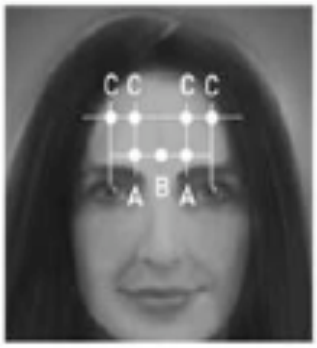
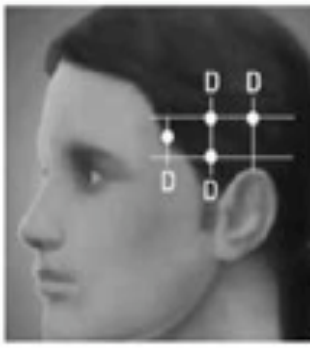
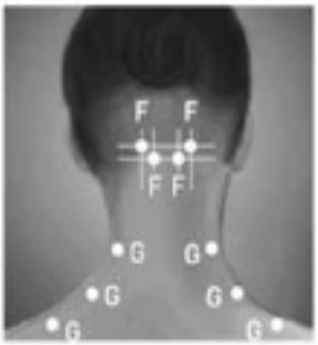
Proven doses and injection sites[1]

Recommended Injection Sites and Doses[1,6]







Order of Injection	Head/Neck Muscle	Recommended Dose (No. of Sites[a])
A	Corrugator[b]	10 Units divided in 2 sites
B	Procerus	5 Units divided in 1 site
C	Frontalis[b]	20 Units divided in 4 sites
D	Temporalis[b]	40 Units divided in 8 sites
E	Occipitalis[b]	30 Units divided in 6 sites
F	Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
G	Trapezius[b]	30 Units divided in 6 sites
TOTAL DOSE		**155 Units**

[a] Each IM injection site = 0.1 mL = 5 Units Botox; [b] Doses distributed bilaterally

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For adult patients with Chronic Migraine.

PRESCRIBING SUMMARY

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses.

INDICATIONS

• Botox® is indicated for the prophylaxis of headaches in adult patients (18 years of age or older) with Chronic Migraine (≥15 days per month with headache lasting 4 hours a day or longer). Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies[6].

PATIENT SELECTION CRITERIA

Summary of Contraindications

• Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.
• Infection at the proposed injection site.
• Patients receiving concomitant treatment of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX could be potentiated.

Use in Special Populations

• Pregnancy: Based on animal data, may cause fetal harm.
• Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the prophylaxis of headaches in chronic migraine.

SAFETY INFORMATION

Summary of Warnings

• Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products.
• Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur.
• Potential serious adverse reactions after BOTOX injections for unapproved uses.
• Concomitant neuromuscular disorder may exacerbate clinical effects of treatment.

Summary of Precautions

• Use with caution in patients with compromised respiratory function.

Adverse Reaction Seriousness and Incidence

• The most common adverse reactions (≥5% and >placebo) are neck pain and headache.

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Established dosing[1].

PRESCRIBING SUMMARY

ADMINISTRATION

Dosage

• The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL. 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 the Table below.

• 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. The recommended retreatment schedule is every 12 weeks.

Head/Neck Muscle	Recommended Dose (No. of Sites[a])
Corrugator[b]	10 Units divided in 2 sites
Procerus	5 Units divided in 1 site
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Occipitalis[b]	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
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TOTAL DOSE	**155 Units**

[a] Each IM injection site = 0.1 mL = 5 Units Botox; [b] Doses distributed bilaterally

Pharmacodynamics

When used for the 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.

Pharmacokinetics

It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. BOTOX is not expected to be presented in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, clinical studies using single fiber electromyographic techniques have shown subtle electrophysiologic findings consistent with neuromuscular inhibition (i.e. "jitter") in muscles distant to the injection site, but these were unaccompanied by any clinical signs or symptoms of neuromuscular inhibition from the effects of botulinum toxin.

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Established safety and efficacy[1].

PRESCRIBING SUMMARY

STUDY REFERENCES

1. Deiner HC, Dodick, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010 Jul; 30(7):804-814.
2. World Health Organization (WHO). Fact Sheet No 277: Headache Disorders. Available from: http://www.who.int/mediacentre/factsheets/fs277/en/ .
3. Natoli JL, Manack A, Dean B, Butler Q, Turkel CC, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010 May; 30(5):599-609.
4. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012 Nov; 16:86-92.
5. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology. 2008 Aug; 71(8):559-556.
6. Allergan, Inc. Botox® Product Monograph. Markham: Allergan, Inc.; 2014.

SUPPLEMENTAL PRODUCT INFORMATION

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products: The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect: Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and upper limb spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur. No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for chronic migraine at the labeled doses have been reported.

Serious Adverse Reactions with Unapproved Use: Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

Hypersensitivity Reactions: Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Pre-Existing Neuromuscular Disorders: Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX.

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Find relief.

SUPPLEMENTAL PRODUCT INFORMATION

Dysphagia and Breathing Difficulties: Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

ADVERSE REACTIONS

The following adverse reactions to BOTOX for injection are discussed in greater detail in other sections of labeling (see Warnings and Precautions): Spread of Toxin Effects, Hypersensitivity, Dysphagia and Breathing Difficulties.

SYMPTOMS AND TREATMENT OF OVERDOSE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see Boxed Warning]. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care. In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm*.

The product monograph for BOTOX (onabotulinumtoxinA) can be obtained on-line at: *http://www.allergan.ca/assets/pdf/ca_botox_pm.pdf*, or directly from Allergan, Inc. at the following address:

Allergan, Inc.
85 Enterprise Blvd., Suite 500
Markham, ON
L6G 0B5 CANADA

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FEWER HEADACHES, MORE RELIEF

Treatment that goes beyond the temporary relief of Chronic Migraine pain

www.botox-migraine.ca

Please note that this is a **mock detail aid that was developed for the course “Medical Writing II: Promotional and Continuing Health Education (Concordia University)”. The data presented was fabricated for the purposes of the assignment, and the information presented does not in any way reflect the views of Allergan Inc.