Injection Workbook for Chronic Migraine

Guidance for identifying BOTOX® candidates, the injection procedure, and discussing treatment with patients

Indication

Chronic Migraine
BOTOX® for injection is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Important Limitations

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.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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 spasticity and at lower doses.

Please see additional Important Safety Information about BOTOX® on following pages.
Introduction

Take the next step in your education with this comprehensive guide to BOTOX® injections. Review Chronic Migraine diagnosis, anatomical assessment, injection technique, patient dialogue, and more.

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PREEMPT® in Phase 3 REsearch Establishing Migraine Prophylaxis Therapy.

Chronic Migraine diagnosis

Practical clinical criteria

15 or more headache days per month
8 or more migraine days per month
4 hours or more per day

Count days when a headache lasted fewer than 4 hours due to successful acute treatment.

Getting to an appropriate diagnosis

1. Uncover true headache frequency.

Ask about headache-free days
Ask how headaches are affecting the patient’s daily life
Ask about migraine features
Use visual cues and open-ended questions to facilitate patient dialogue

2. Document headache frequency, severity, and disability.

Headache diaries
Intake forms
Validated measurement tools

3. Clearly communicate a diagnosis.

“You have Chronic Migraine”

IMPORTANT SAFETY INFORMATION (continued)

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

IMPORTANT SAFETY INFORMATION (continued)

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. Please see additional Important Safety Information about BOTOX® on following pages.
Chronic Migraine diagnosis

Many appropriate patients do not receive a Chronic Migraine diagnosis

36%

Chronic Migraine diagnosis rate for patients who meet the criteria and are seeing a specialist.

25%

Chronic Migraine diagnosis rate for patients who meet the criteria and are seeing any healthcare professional.

Possible reasons why clinicians don’t diagnose Chronic Migraine sooner

Don’t see an urgent benefit to providing a patient with a specific diagnosis

Feel documentation of a Chronic Migraine diagnosis is only required when seeking BOTOX® prior authorization

May classify some migraines as tension-type headaches, leading to a diagnosis of mixed headache disorder

Don’t see Chronic Migraine as physiologically distinct from other headache types

BOTOX® patients don’t receive a formal Chronic Migraine diagnosis until their first treatment

4 in 10

Based on claims data from 19,727 Chronic Migraine patients.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Spread of Toxin Effect

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for Chronic Migraine at the labeled dose 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.

Please see additional Important Safety Information about BOTOX® on following pages.
Chronic Migraine diagnosis

Why diagnose? Survey results among patients with varying conditions show that patients want to know:

- **99%** stated that they want to learn about their condition*
- **95%** feel that being well-informed will have a positive effect on their treatments*

Diagnosis can set the stage for a comprehensive management plan**

- Increases patient understanding about their disease
- Highlights the importance of appropriate preventive treatment and management of comorbidities/medication overuse
- Supports discussions about Chronic Migraine-specific treatment options like BOTOX®

*Based on a study of 432 patients.
**N = 337 patients with various conditions.

Patients with both tension headache and migraine may not have mixed headache disorder**

- **90%** of patients with disabling tension headaches actually had a form of migraine.* This may lead some clinicians to misclassify patients who actually have Chronic Migraine

The nature of migraine attacks may obscure a patient’s true headache and lead to a misdiagnosis:

- **4 to 72 hours**
- **5 to 60 minutes**
- **24 to 48 hours**

Patients may not count dull headaches that may accompany postdrome as part of their headache day tally, because they are less severe. This could lead to underdiagnosis of Chronic Migraine.**

*Based on a study of 432 patients.
**N = 337 patients with various conditions.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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.

**Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders**

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction 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® (see Warnings and Precautions).

Please see additional Important Safety Information about BOTOX® on following pages.
Chronic Migraine is a distinct disease

Chronic Migraine is a clinically and physiologically distinct disease

<table>
<thead>
<tr>
<th></th>
<th>Episodic Migraine</th>
<th>Chronic Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average headache duration per attack (without medication)</td>
<td>38.8 hours</td>
<td>65.1 hours</td>
</tr>
<tr>
<td>MIDAS Grade IV (≥ 21)</td>
<td>23.6%</td>
<td>79.1%</td>
</tr>
<tr>
<td>Visit emergency room%</td>
<td>5.4% per year</td>
<td>9.0% per year</td>
</tr>
<tr>
<td>Anxiety</td>
<td>18.8%</td>
<td>30.2%</td>
</tr>
<tr>
<td>Depression</td>
<td>25.6%</td>
<td>41.2%</td>
</tr>
<tr>
<td>Obesity</td>
<td>21.0%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Associated structural changes in the brain</td>
<td>Possible</td>
<td>Likely</td>
</tr>
</tbody>
</table>

*Chronic Migraine n = 499; episodic migraine n = 8227.
†MIDAS = The Migraine Disability Assessment Test
‡Chronic Migraine n = 655; episodic migraine n = 17,249.
§Incidence of comorbidity.
ǁEpisodic migraine is characterized by migraine patients who experience 0 to 14 headache days per month, some of which may be migraine.

A holistic examination of this distinct disease can help inform Chronic Migraine diagnosis

- Evaluate headache history beyond a 1 month to 3 months time frame
- Encourage patients to include postdrome as part of their headache day count
- Ask open-ended questions to uncover disability and comorbidities
- Understand the persistent physiological changes associated with Chronic Migraine

Chronic Migraine is associated with persistent physiological changes

Physiological changes associated with Chronic Migraine include structural changes in the brain such as iron accumulation in the periaqueductal gray matter. These changes can be shown in functional MRI imaging.

These images are based on a functional imaging study of 120 people. The MRI images compare Chronic Migraine vs episodic migraine patients, and were taken when they were not experiencing migraine. The study’s primary finding is that brain cortical surface area, thickness, and regional volumes are accurate markers for classifying migraine patients as having Chronic Migraine vs episodic migraine.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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 (see Boxed Warning).

Please see additional Important Safety Information about BOTOX® on following pages.
Identifying BOTOX® candidates

Considerations when evaluating treatment plans

Prevention may be an important part of a Chronic Migraine management plan. Aside from ensuring adequate prevention, a management plan may include optimizing acute medication use/limiting medication overuse, addressing comorbid conditions, and adjusting patient lifestyles (eg, diet, exercise, curbing caffeine overuse).11

Treatment planning begins with a thorough history, which can include inquiry around these topics:

- Is the patient using more acute medications than recommended?
- What treatments has the patient tried with other providers?
- Is the patient meeting treatment goals?
- Is the patient re-trying a preventive treatment at a different dose?
- Is the patient following his/her prescribed treatment regimen as recommended?

Your patients may already meet their insurance policy requirements for BOTOX® treatment

Majority of lives require trial of 2 or fewer oral preventives22,23

Chronic Migraine patients have tried

77.5% 12.8% 9.7% 2 or fewer 0 or more N/A preventive treatments on average (n = 493)24

Understanding oral preventive trial requirements

Some factors considered when determining adequate treatment trial include:
- Number of oral preventives needed
- Types of therapeutic classes
- Required duration of each treatment trial (if any)
- Whether medications with contraindications or intolerance concerns may count as a treatment trial

Check with individual payer policies for specific treatment trial requirements.

*As of Q2 2015.

Based on data covering 244,831,608 medical lives.

Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eye lid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), muscularoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), muscularoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 1%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX® treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients.

Please see additional Important Safety Information about BOTOX® on following pages.
BOTOX® efficacy was achieved following the proven PREEMPT Paradigm

Patients on BOTOX® had 8 to 9 fewer headache days and migraine/probable migraine days per month compared with baseline (vs 6 to 7 days with placebo) at 24 weeks.1,21,22

RESULTS FROM PREEMPT 1,25

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
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<th>28</th>
<th>32</th>
<th>36</th>
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<th>44</th>
<th>48</th>
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<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
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<td>a</td>
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<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Placebo (n = 338)</td>
<td>a</td>
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<td>a</td>
<td>a</td>
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<td>a</td>
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</table>

*P ≤ .05

RESULTS FROM PREEMPT 21,22

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<th>Week</th>
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<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
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<th>36</th>
<th>40</th>
<th>44</th>
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<tbody>
<tr>
<td>BOOTOX® (n = 347)</td>
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<td>a</td>
<td>a</td>
<td>a</td>
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<td>a</td>
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<td>a</td>
</tr>
<tr>
<td>Placebo (n = 358)</td>
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<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
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<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

*P ≤ .05

In PREEMPT trials, BOTOX® patients received at least 2 treatments, 12 weeks apart, to determine effectiveness (primary end point was at 24 weeks).

Please see additional Important Safety Information about BOTOX® on following pages.
Responder rates for BOTOX® patients in PREEMPT clinical trials

### 50% reduction in headache days from baseline in each month at week 24

**RESULTS FROM PREEMPT 1**

<table>
<thead>
<tr>
<th></th>
<th>% of Patients With a ≥ 50% Decrease From Baseline in Headache Days (Out of 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX® (N = 341)</td>
<td>44%</td>
</tr>
<tr>
<td>Placebo (N = 338)</td>
<td>36%</td>
</tr>
</tbody>
</table>

\*P = NS

**RESULTS FROM PREEMPT 2**

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<tr>
<th></th>
<th>% of Patients With a ≥ 50% Decrease From Baseline in Headache Days (Out of 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX® (N = 347)</td>
<td>51%</td>
</tr>
<tr>
<td>Placebo (N = 356)</td>
<td>34%</td>
</tr>
</tbody>
</table>

\*P < .001

Significant difference in BOTOX® vs placebo in PREEMPT 2 but not PREEMPT 1.

- Responder rate data based on “Other” end point in PREEMPT clinical trials.

**Study design:** PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Primary time point was 24 weeks. Subjects included adult Chronic Migraine patients (who in a 28-day baseline period had at least 15 headache days lasting 4 hours or more, with at least 50% being migraine/probable migraine.

### 75% reduction in headache days from baseline in each month at week 24

**RESULTS FROM PREEMPT 1**

<table>
<thead>
<tr>
<th></th>
<th>% of Patients With a ≥ 75% Decrease From Baseline in Headache Days (Out of 100%)</th>
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<tbody>
<tr>
<td>BOTOX® (N = 341)</td>
<td>19%</td>
</tr>
<tr>
<td>Placebo (N = 338)</td>
<td>15%</td>
</tr>
</tbody>
</table>

\*P = NS

**RESULTS FROM PREEMPT 2**

<table>
<thead>
<tr>
<th></th>
<th>% of Patients With a ≥ 75% Decrease From Baseline in Headache Days (Out of 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX® (N = 347)</td>
<td>26%</td>
</tr>
<tr>
<td>Placebo (N = 356)</td>
<td>16%</td>
</tr>
</tbody>
</table>

\*P = .002

Significant difference in BOTOX® vs placebo in PREEMPT 2 but not PREEMPT 1.

- Responder rate data based on “Other” end point in PREEMPT clinical trials.

**Study design:** PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Primary time point was 24 weeks. Subjects included adult Chronic Migraine patients (who in a 28-day baseline period had at least 15 headache days lasting 4 hours or more, with at least 50% being migraine/probable migraine.

**IMPORTANT SAFETY INFORMATION**

**DRUG INTERACTIONS (continued)**

Co-administration of BOTOX® or other agents interfering with neuromuscular transmission (e.g., aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects.

**IMPORTANT SAFETY INFORMATION (continued)**

**DRUG INTERACTIONS (continued)**

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin and also by administration of a muscle relaxant before or after administration of BOTOX®.

Please see accompanying full Prescribing Information including Boxed Warning and Medication Guide.
PREEMPT Paradigm overview

The PREEMPT Paradigm is based on 10 years of studies to assess patient type, muscle selection, dose, and treatment interval. Departures from the approved paradigm may lead to efficacy results and adverse events different from those seen in the clinical trials.

Summary of dose by area

<table>
<thead>
<tr>
<th>MUSCLE AREA</th>
<th>RECOMMENDED DOSE/NUMBER OF SITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrugator</td>
<td>10 Units divided between 2 sites</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 Units in 1 site</td>
</tr>
<tr>
<td>Frontalis</td>
<td>20 Units divided between 4 sites</td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 Units divided between 8 sites</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 Units divided between 6 sites</td>
</tr>
<tr>
<td>Cervical paraspinal</td>
<td>20 Units divided between 4 sites</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 Units divided between 6 sites</td>
</tr>
<tr>
<td>TOTAL DOSE</td>
<td>155 Units divided between 31 sites</td>
</tr>
</tbody>
</table>

*Retreatment after 24 weeks should be determined per clinician’s discretion.
†Document and discard the 45-Unit wastage.

**IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING**

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.

**STANDARD METHODS REGARDLESS OF AREA**

- For each injection, the injection volume will be 0.1 mL (equivalent to 5 Units)
- Consider injecting in the most superficial aspect of the muscle
- Evaluate the anatomy, including relevant function and the effects of treatment on these muscles
- Recognize unique anatomy, as no 2 patients are alike; focus on the muscle, not measurements, to adjust for individual anatomical variations
- Consider location, depth, and angle carefully, as the site of medication delivery may be different from the needle insertion point
  - Injection sites depicted in diagrams represent delivery point of the medication

**BEFORE INJECTION**

- Verify the needle is securely fastened to the injection syringe
- Line up the bevel of the needle with the gradations on the syringe so the bevel is facing upward; this will help you more easily orient the bevel of the needle when injecting

**DURING INJECTION**

- Inject on 1 side first for bilateral injections, then proceed to the other side and repeat
- Consider changing needles frequently to reduce patient discomfort; consider using 1 needle per area or changing every 4 to 6 sites
- Inject with the bevel up, pointing away from the skin
- It may be helpful to hold the hub of the needle with 1 hand to ensure the needle does not twist
  - Push the plunger with the other hand to administer the medication
- Aspirate to ensure no blood return
- Target the muscle—The needle should be inserted through the epidermis/dermis layer, which may feel more rigid when penetrated. The injection should be given just when there is a decrease in resistance, avoiding the periosteum. This decrease in resistance may be subdermal, not intramuscular

**IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING (continued)**

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 spasticity at all lower doses.

Please see additional Important Safety Information about BOTOX® on following pages.
Anatomy of the face and head

**Frontalis**
Originates from the epicranial aponeurosis, and attaches distally to the skin of the forehead and eyebrow.

**Corrugator**
Attaches to the nasal-frontal bone medially and the skin of the eyebrow laterally.

**Procerus**
Originates from the aponeurotic fascia of the nose and inserts into the glabellar skin.

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Interrelationship between muscles
- Corrugator muscle fibers and frontalis muscle fibers interdigitate in the region of the medial brow where the corrugator inserts into skin.
- On the corrugator’s medial aspect, it is deep to both the procerus muscle and the superficial, thinned-out frontalis muscle fibers.

*Muscles and anatomical structures shown for anatomical reference only.

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Indication
**Chronic Migraine**
BOTOX® for injection is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Important Limitations
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.

**CONTRAINDICATIONS**
BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

Please see additional Important Safety Information including Boxed Warning about BOTOX® on following pages.
Anterior injections (continued)*

**Functional anatomy**

The **frontalis muscle** is a brow elevator, pulling the brow upward.\(^3\)\(^8\) Weakening of this muscle may result in brow ptosis.

Activating the frontalis creates transverse lines on the forehead (Figure 1).\(^8\)

The **corrugator muscle** is a brow depressor, pulling the brow downward.\(^3\)\(^8\) Weakening of this muscle may elevate the brow.

Activating the corrugator creates vertical lines between the brow (Figure 2).\(^8\)

**Functional anatomy (continued)**

The **procerus muscle** draws down the medial aspect of the brow.\(^8\)

Activating the procerus creates a transverse ridge over the nose (Figure 3).\(^8\)

The **temporalis** is a masticatory muscle. Clenching the teeth activates the temporalis and can help localize the muscle (Figure 4).\(^8\)

*Muscles and anatomical structures shown for anatomical reference only.

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**IMPORTANT SAFETY INFORMATION (continued)**

**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**

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX**® for Chronic Migraine at the labeled dose have been reported.

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**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.

Please see additional Important Safety Information about **BOTOX**® on following pages.
Standard corrugator PREEMPT protocol*

Dose
- 5 Units (0.1 mL) in each site
- Total of 10 Units divided into 2 sites

**Corrugator injection sites**

- Medial inferior edge of the superior orbital rim

**Corrugator muscle**

**Injection site**
- About 1.5 cm (~1 fingerbreadth) above the medial inferior edge of the superior orbital rim (bony landmark). This may vary based on individual anatomy.

**Additional factors to consider prior to injection**
- Ask the patient to furrow the brow, which activates the corrugator and causes medial and inferior movement of the brow
- Palpate and pinch the muscle, holding between the thumb and index finger (Figure 5)
- Consider injecting at a 90º angle into the belly of the muscle, remaining above the periosteum, to help ensure medication delivery into the corrugator and not into a nearby muscle (Figure 5)
- Because facial anatomy is different, the standard measurements for some patients may lead to inadvertent penetration of the frontalis muscle, which may lead to brow ptosis
- corrugator muscles are thin, so injecting too deep can hit the periosteum and may trigger headache/migraine
- Injecting with the needle pointed upward and laterally at a 45º angle may increase the risk of frontalis penetration

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

**IMPORTANT SAFETY INFORMATION** (continued)
**WARNINGS AND PRECAUTIONS** (continued)

**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.

**Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders**
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction 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® (see Warnings and Precautions).

Please see additional Important Safety Information about BOTOX® on following pages.
Standard procerus PREEMPT protocol*

**Dose**
- 5 Units (0.1 mL) in 1 site
- Total of 5 Units

**Injection site**
- The base of the procerus resides approximately midway between the 2 corrugator injections

**Medial inferior edge of the superior orbital rim**

**Procerus muscle**

**Procerus injection site**

**Additional factors to consider prior to injection**
- Ask the patient to furrow the brow; use the vertical and horizontal lines as orientation sites
- Inject into the belly of the muscle at 90° to deliver medication into the procerus and not a nearby muscle (eg, frontalis) (Figure 6)
- The procerus muscle is thin, so injecting too deep can hit the periosteum
- Injecting too high in the brow area, in the lower frontalis instead of the procerus, can lead to brow ptosis

Be mindful of the thin muscles of the forehead and brow. Stay in the most superficial aspect of the muscle to avoid hitting the periosteum.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**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 (see Boxed Warning).

**Human Albumin and Transmission of Viral Diseases**
This product contains 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

Please see additional Important Safety Information about BOTOX® on following pages.
Standard frontalis PREEMPT protocol*

**Dose**
- 5 Units (0.1 mL) in each site
- Total 20 Units divided into 4 sites

**Medial injection site**
- Visually, draw a vertical line up from the medial inferior edge of the superior orbital rim
- Medial injection is generally within the upper one-third of the forehead, and at least 1.5 cm (~1 fingerbreadth) above the corrugator injection site. This may vary based on individual anatomy

**Lateral injection site**
- Lateral injections are parallel, lining up with the lateral limbus of the cornea, and at least 1.5 cm (~1 fingerbreadth) lateral to the medial injection site (Figure 7). This may vary based on individual anatomy

**Additional factors to consider prior to injection**
- Angle the needle superiorly at 45º (Figure 8)
- Frontalis muscles are thin, so inject in the most superficial aspect of the muscle to avoid the periosteum
- Injecting in the frontalis too low may cause medial brow weakness and lateral brow elevation; the elevation occurs as a compensatory mechanism to keep the eyelids open in the presence of medial brow weakness
- Weakening the frontalis may exacerbate preexisting brow ptosis; counsel patients with this condition accordingly (see page 42)
- Consider that injection points are different than medication delivery points
- If patients are concerned about discomfort, the injector may consider a topical anesthetic in this area
- Account for individual anatomy. Forehead sizes are different, so generally stay within the upper one-third of the forehead.

*Muscles and anatomical structures shown for anatomical reference only.
* This is a hypothetical patient.

**Important Safety Information (continued)**

**Adverse Reactions**
Adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: **Boxed Warning**, **Contraindications**, and **Warnings and Precautions**.

Please see additional Important Safety Information about BOTOX® on following pages.
Standard temporalis PREEMPT protocol*

Dose
• 5 Units (0.1 mL) in each site
• Total 40 Units divided into 8 sites (4 on each side of head)

Injection site
• Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm (≈ 2 fingerbreadths)

Injection site
• Move about 1.5 cm to 3 cm (≈ 1 to 2 fingerbreadths) up from the first injection, still in line with the tragus of the ear

Injection site
• Move about 1.5 cm to 3 cm (≈ 1 to 2 fingerbreadths) forward, toward the face, from the first and second injections. Make the third injection halfway vertically between injection sites 1 and 2

Injection site
• Move about 1.5 cm (≈ 1 fingerbreadth) back from the second injection, and in line with the midportion (helix) of the ear

Additional factors to consider prior to injection
• Inject the most superficial aspect of the muscle at 45º (Figure 9)
• Aspirate to ensure no blood return
• Keep injections within the hairline, particularly for the most anterior injection site; the needle should be angled posteriorly (Figure 9)
• Clenching the teeth activates the temporalis and can help localize the muscle
• Area may be prone to bleeding. Apply pressure immediately and manage before the patient leaves
• A finger can be placed on the middle of the helix of the ear to guide the fourth injection
• The temporalis is covered by a thick fascia made up of fibrous bands, and patients may hear the injection needle passing through this fascia

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

*Muscles and anatomical structures shown for anatomical reference only.

Please see additional Important Safety Information about BOTOX® on following pages.
Posterior injections*

**Muscles of the neck and posterior head**

- **Occipitalis**—Originate at the highest nuchal line and inserts into the epicranial aponeurosis, which is attached to the frontalis\(^3\)
- **Cervical paraspinal** muscles should be considered a group (including the splenius capitis and semispinalis capitis) running deep alongside the cervical spine\(^3\)
- **Trapezius**—A flat, triangular muscle situated over the back of the neck and upper thorax\(^3\)

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**Functional anatomy**

- One function of the **occipitalis** is as an anchor for the frontalis\(^3\)
- **Cervical paraspinal** muscles stabilize and allow for movement of the head and cervical spine (Figure 10)\(^3\)
- In addition to the muscles that are deep to the trapezius, the **trapezius** functions to stabilize and bend the head and neck backward and laterally (Figure 11)\(^3\)

*This is a hypothetical patient.

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**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS (continued)**

**Chronic Migraine (continued)**

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX® treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients.

**Postmarketing Experience**

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

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**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS (continued)**

**Postmarketing Experience (continued)**

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been 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 cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

Please see additional Important Safety Information about BOTOX® on following pages.
Standard occipitalis PREEMPT protocol*

Dose
- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

Injection site 1
- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 12, page 33)
- Locate the tip of the mastoid process behind the ear (Figure 12, page 33)
- Place your thumb on the midpoint of the occipital protuberance (inion) and your index finger on tip of the mastoid process
- Divide the space between your thumb and index finger in half
- Place the first injection just above the nuchal ridge at this midpoint

Injection site 2
- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 28) for the second muscle area for injection (eg, at the 10 o’clock position for the left injection)

Injection site 3
- Measure a diagonal fingerbreadth up and medial for the third muscle area for injection (eg, at the 2 o’clock position for the left injection)

**Occipitalis injection sites**

**Dose**
- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

**Injection site 1**

- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 12, page 33)
- Locate the tip of the mastoid process behind the ear (Figure 12, page 33)
- Place your thumb on the midpoint of the occipital protuberance (inion) and your index finger on tip of the mastoid process
- Divide the space between your thumb and index finger in half
- Place the first injection just above the nuchal ridge at this midpoint

**Injection site 2**

- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 28) for the second muscle area for injection (eg, at the 10 o’clock position for the left injection)

**Injection site 3**

- Measure a diagonal fingerbreadth up and medial for the third muscle area for injection (eg, at the 2 o’clock position for the left injection)

**Occipitalis injection sites**

**Additional factors to consider prior to injection**

- The occipitalis muscle is shallow
- Inject the most superficial aspect of the muscle, which will be just upon penetration of the dermis (Figure 13)
- Inject at 45º, angling the needle upward and away from the neck (Figure 13)
- Injecting too low in the neck may result in neck pain and weakness; inject above the nuchal ridge

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

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**IMPORTANT SAFETY INFORMATION (continued)**

**DRUG INTERACTIONS**

Co-administration of BOTOX® or other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects.

Please see additional Important Safety Information about BOTOX® on following pages.
IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS (continued)

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin and also by administration of a muscle relaxant before or after administration of BOTOX®.

Injection site 1

• Measure about 1 cm left of the midline of the cervical spine and about 3 cm (~2 fingerbreadths) inferior to the lower border of the occipital protuberance

Injection site 2

• Measure about 1.5 cm (~1 fingerbreadth) diagonally up at a 45º angle toward the helix of the ear (see diagram on page 28) from the first injection site

Cervical paraspinal injection sites*

1 2 3 4

Additional factors to consider prior to injection

• Assess patient for preexisting neck pain/weakness to help properly set expectations about this muscle group

• Position the patient upright, with the head in a neutral position; flexing far forward may result in injecting too deep

• Visualize a line across the neck, ~2 fingerbreadths down from the occipital protuberance, and avoid injecting below that line (Figure 14)

• Inject higher (in the hairline) to help minimize the potential for neck weakness—consider the area the suboccipitals region

• Inject in the most superficial aspect of the muscle, angling 45º and superiorly

• Penetrating the fascia should be sufficient to avoid injecting too deep

• Cervical paraspinal muscles are a group of muscles running deep to the cervical spine (see posterior anatomy on page 30 for details)

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

Please see accompanying full Prescribing Information including Boxed Warning and Medication Guide.
Standard trapezius PREEMPT protocol*

Dose
- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

Injection site
- Divide the upper portion of the trapezius muscle in half, from the inflection point of the neck (necklace line) to the acromioclavicular joint
- The first injection is located at this midpoint

Injection site
- Split the difference between injection 1 and the acromioclavicular joint

Injection site
- Split the difference between injection 1 and the necklace line

Trapezius injection sites

Acromioclavicular joint
Inflection point of neck (necklace line)
Trapezius muscle

Additional factors to consider prior to injection
- Assess patient for possible preexisting neck/shoulder weakness to help properly set expectations about injecting this muscle
- Inject horizontal to the muscle to avoid injecting too deep (Figure 15)
- Inject the supraclavicular portion of the muscle, lateral to the neckline and medial to the deltoid/acromioclavicular joint (Figure 15)
- Injecting too high into the cervical spine area or too deep may lead to neck weakness, pain, and compensatory muscle activity
- Patients with small frames may be predisposed to weakness in this area

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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 ascension, 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.

Please see additional Important Safety Information about BOTOX® on following pages.
Adverse reactions ≥ 5% in Chronic Migraine clinical trials were headache and neck pain (n = 687).

Adverse reactions reported by ≥ 2% of patients treated with BOTOX® and more frequent than in placebo-treated patients in 2 Chronic Migraine double-blind, placebo-controlled trials.

### Adverse Reactions by Body System

<table>
<thead>
<tr>
<th>Adverse Reactions by Body System</th>
<th>BOTOX® 155 Units to 195 Units (n = 687)</th>
<th>Placebo (n = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32 (5%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>26 (4%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye disorders:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (4%)</td>
<td>2 (&lt; 1%)</td>
</tr>
<tr>
<td>Infections and infestations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (3%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (9%)</td>
<td>19 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (4%)</td>
<td>2 (&lt; 1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (3%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>General disorders and administration-site conditions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>23 (3%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Vascular disorders:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (2%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

### Discontinuation rates due to adverse events

- 4% (26/687) BOTOX® vs 1% (8/692) Placebo

- Observed treatment-related adverse events were typically mild to moderate in severity
- The most frequent adverse events leading to discontinuation in the BOTOX® group were neck pain, headache, worsening migraine, muscular weakness, and eyelid ptosis

**Indication**

Chronic Migraine

BOTOX® for injection is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

**Important Limitations**

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (1-4 headache days or fewer per month) in 7 placebo-controlled studies.

**IMPORTANT SAFETY INFORMATION (continued)**

**CONTRAINDICATIONS**

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin or to any of the components in the formulation.

Please see additional Important Safety Information about BOTOX® on following pages.
Patient case study 1*

Preexisting ptosis in a new patient consult†

Figure 16
Patient with ptosis*

Background

• 58-year-old BOTOX® candidate
• Tried 3 previous oral preventive medications before BOTOX® was considered
• Awaiting first BOTOX® injection
• He may not be aware of ptosis, especially with compensatory activity

How would you approach injecting this patient?

Any patient assessment and injection technique considerations discussed will not eliminate the risk of ptosis following BOTOX® injections. There was a 4% incidence of eyelid ptosis and a 2% incidence of facial paresis for BOTOX® patients in PREEMPT clinical trials.†

†Muscles and anatomical structures shown for anatomical reference only.

*Though based on real-world clinical experience and PREEMPT clinical trial findings, these case studies are hypothetical. They were created for discussion purposes only. Please consider your own experience and clinical judgment when assessing, injecting, and managing BOTOX® for Chronic Migraine patients.

Patient case study 2*

Medial brow ptosis and lateral brow elevation in returning patient†

Before BOTOX® injection
6 weeks after BOTOX® injection

Background

• 38-year-old BOTOX® user
• 6 weeks after her most recent injection, she noticed medial brow ptosis and lateral brow elevation
• Wants to continue BOTOX® treatment but is worried about worsening ptosis

What are the considerations for this patient to help ensure appropriate re-treatment?

Any patient assessment and injection technique considerations discussed will not eliminate the risk of medial brow ptosis and/or lateral brow elevation following BOTOX® injections. There was a 4% incidence of eyelid ptosis and a 2% incidence of facial paresis for BOTOX® patients in PREEMPT clinical trials.†

†Muscles and anatomical structures shown for anatomical reference only.

IMPORTANT SAFETY INFORMATION (continued)
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.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Spread of Toxin Effect
See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for Chronic Migraine at the labeled dose have been reported. Please see additional Important Safety Information about BOTOX® on following pages.
Before any injections occur, patients should be evaluated for conditions that may be affected or exacerbated by treatment. If any conditions are found to exist, the injector should inform and counsel the patient. Proper counseling will help set patient expectations. Patients with preexisting conditions should be carefully assessed to determine if they’re appropriate for injection.

**PATIENT EXAMINATION:**
- Visualy inspect the muscle
- Ask the patient to activate the muscle
- Palpate the muscle

**Preexamination of the brow**

*What to look for:*
Inspect for excessive soft tissue resting near the upper lid of the eye and lid drooping (Figure 18).

**Preexamination of the forehead**

*What to look for:*
Brow ptosis, possibly compensated by active frontalis muscles, of which the patient may be unaware.

*How to examine:*
Ask the patient to activate the frontalis muscle by raising and lowering the eyebrows (Figure 23). Observe the dynamic muscle activity and whether there is any compensatory mechanism keeping the eyelids open in the presence of brow weakness.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**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.

*Please see additional Important Safety Information about BOTOX® on following pages.*
Patient assessment before injection (continued)*

Preexamination of the neck

What to look for: Neck pain and neck weakness may be present among Chronic Migraine patients. Inspect the patient for a head-forward position, which may indicate preexisting muscle weakness (Figure 24).

How to examine: Observe the patient, standing, in profile with a neutral-spine position. Look for a plumb (vertical) line from the tragus and anterior ridge of the trapezius through the patient's center of gravity (Figure 25). If the tragus is anterior to this line by 2 to 3 fingerbreadths, this may be abnormal (Figure 24).

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction 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® (see Warnings and Precautions).

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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 (see Boxed Warning).

Please see additional Important Safety Information about BOTOX® on following pages.
Tips to efficiently administer BOTOX® treatment in the office

Office staff and processes:

- Assign staff to specific roles
  - Roles include ordering BOTOX® and submitting insurance verifications, prior authorizations, and claims

- Have a process to identify Chronic Migraine patients
  - Use a headache diary, screener, intake form, and/or symptom assessment tool to document symptoms and medication history

- Use a system to track and schedule recurring BOTOX® treatment
  - Ensure patients receive treatment every 12 weeks
  - Send reminders 1 to 2 weeks before the appointment

- Set up BOTOX® Clinic Days from the beginning
  - May improve patient access and the efficiency of paperwork processing by having a dedicated time and place for procedures

- Consider involving additional office staff to help
  - Include NPs/PAs for follow-ups, patient counseling, and injections, as appropriate
  - Train nursing staff to reconstitute and prepare syringes for BOTOX® treatment

Insurance documentation requirements:

Consult individual policies for specific requirements for BOTOX®. Generally, you may need the following for insurance purposes:

- Medication history
- Defined medical necessity
- Services provided
- BOTOX® administration details (sites, units, schedule)
- Clinical effectiveness and/or outcomes of BOTOX® therapy

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Human Albumin and Transmission of Viral Diseases

This product contains 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

Adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Boxed Warning, Contraindications, and Warnings and Precautions.

Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscle weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (5% vs 2%), musculoskeletal pain (5% vs 1%), myalgia (5% vs 1%), facial parasthesia (2% vs 0%), hypertension (2% vs 1%), and muscle spasm (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX® treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients.

Please see additional Important Safety Information about BOTOX® on following pages.
Resources available to your patients

Patient education and financial assistance

- Patient education brochures
  - Introduction to treatment for patients considering BOTOX® as their next step (also available in Spanish)
  - Information to help patients understand what to expect when starting treatment

- Patient support program
  - Patients can register at BOTOXChronicMigraine.com to receive treatment reminders and healthy-living tips

- Patients may pay as little as $0 for BOTOX® treatments
  - Here’s how:
    - Most insurance plans cover the majority of BOTOX® costs*
    - On average, patients pay $161 out of pocket for BOTOX® for Chronic Migraine, but with the BOTOX® Savings Program, eligible patients can receive reimbursement to help with these remaining costs†‖§

- There should be no financial barriers to patients accessing BOTOX® treatment.
  - Visit BOTOXSavingsProgram.com to get started.

- Program Terms, Conditions, and Eligibility Criteria
  1. This offer is good for use only with a valid prescription for BOTOX® (onabotulinumtoxinA).
  2. Based on insurance coverage, Chronic Migraine patients can receive up to $3500 per treatment, up to $1750 per year for up to 5 treatments in 2018. Patients must be commercially insured and meet eligibility criteria to qualify. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs. Please see terms and conditions.
  3. This offer is not valid for use by patients enrolled in Medicare, Medicaid, or other federal or state programs (including any state pharmaceutical assistance programs), or private indemnity or HMO insurance plans that reimburse you for the entire cost of your prescription drugs. Patients may not use this offer if they are Medicare-eligible and enrolled in an employer sponsored health plan or prescription drug benefit program for retirees. This offer is not valid for cash-paying patients.
  4. This offer is valid for up to 18 treatments per year. Offer expires only on treatment received before the program expires on 12/31/18.
  5. Offer is valid only for BOTOX® and BOTOX® treatment-related costs not covered by insurance.
  6. A BOTOX® Savings Program check will be provided upon approval of a claim. The claim must be submitted with treatment details from an Explanation of Benefits (EOB) or a Specialty Pharmacy Provider (SPP) receipt.
  7. A BOTOX® Savings Program Program check may be sent either directly to you or to your selected healthcare provider who provided treatment. For payment to be made directly to your healthcare provider, you must authorize an assignment of benefit during each claim submission. You are not obligated to assign your BOTOX® Savings Program benefit to your healthcare provider to participate in the program.

- Additional resources

- Patient support program
  - Questions about this program, please call 1-800-44-BOTOX.

- Business Practice Specialists
  - A Business Practice Specialist (BPS) can help answer your questions about BOTOX® patient access and reimbursement.

- Online videos and education at BOTOXAcademy.com
  - Register for ongoing education and to download tools for your office.

- Resources available to injectors and the office

- Peer-to-peer training
  - Preceptorships, proctorships, and advanced group workshops are available to help improve your injection technique.

- Resources available to patients

- **Additional resources**

- **Patient education and financial assistance**

- **Patient support program**

- **Program Terms, Conditions, and Eligibility Criteria**
  1. This offer is good for use only with a valid prescription for BOTOX® (onabotulinumtoxinA).
  2. Based on insurance coverage, Chronic Migraine patients can receive up to $3500 per treatment, up to $1750 per year for up to 5 treatments in 2018. Patients must be commercially insured and meet eligibility criteria to qualify. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs. Please see terms and conditions.
  3. This offer is not valid for use by patients enrolled in Medicare, Medicaid, or other federal or state programs (including any state pharmaceutical assistance programs), or private indemnity or HMO insurance plans that reimburse you for the entire cost of your prescription drugs. Patients may not use this offer if they are Medicare-eligible and enrolled in an employer sponsored health plan or prescription drug benefit program for retirees. This offer is not valid for cash-paying patients.
  4. This offer is valid for up to 18 treatments per year. Offer expires only on treatment received before the program expires on 12/31/18.
  5. Offer is valid only for BOTOX® and BOTOX® treatment-related costs not covered by insurance.
  6. A BOTOX® Savings Program check will be provided upon approval of a claim. The claim must be submitted with treatment details from an Explanation of Benefits (EOB) or a Specialty Pharmacy Provider (SPP) receipt.
  7. A BOTOX® Savings Program Program check may be sent either directly to you or to your selected healthcare provider who provided treatment. For payment to be made directly to your healthcare provider, you must authorize an assignment of benefit during each claim submission. You are not obligated to assign your BOTOX® Savings Program benefit to your healthcare provider to participate in the program.

- **Important Safety Information (continued)**

- **Adverse Reactions (continued)**

- **Postmarketing Experience**

- **Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).**

- There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been 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 cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

- Please see Important Safety Information, including Boxed Warning, about BOTOX® throughout this brochure.

- **For questions about this program, please call 1-800-44-BOTOX.**
Helpful phone numbers and websites

ORDERING
AllerganDirect.com or call 1-800-44-BOTOX (1-800-444-8699)

CUSTOMER SERVICE
1-800-44-BOTOX (1-800-444-8699)

ALLERGAN MEDICAL INFORMATION LINE
1-800-433-8871

PATIENT FINANCIAL ASSISTANCE
For commercially insured patients: BOTOX Savings Program.com

PROFESSIONAL EDUCATION & RESOURCES
For injection training opportunities: Contact your Allergan representative
For Business Practice Specialists: Contact your Allergan representative
For injection and reconstitution videos, plus downloadable patient education and more: BOTOX Academy.com

Please see Important Safety Information, including Boxed Warning, inside.