Chronic Migraine

Injection Workbook

Guidance for identifying BOTOX® (Botulinum Toxin Type A) candidates, the injection procedure, and discussing treatment with patients

BOTOX® for injection is indicated for the management of symptom relief in adults fulfilling criteria for chronic migraine (headaches on ≥15 days per month of which at least 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications.[1]

For full indication for the product and further information, please refer to Botox® approved Israel Prescribing Information.

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INTRODUCTION

This workbook is designed to help you learn and apply the proven BOTOX® Injection Paradigm. It also contains information to help injectors identify appropriate BOTOX® candidates, understand procedure-related anatomy and manage patient expectations.

Important safety information: Contraindications

BOTOX® is contraindicated:
- In individuals with known hypersensitivity to botulinum toxin A or to any of the excipients listed in Botox® Israeli Product Information.[1]
- in the presence of infection at the proposed sites.

Table of contents

Identifying BOTOX® candidates

Practical clinical criteria for Chronic Migraine diagnosis[1,2]

- With or without medication overuse[2]

≥15
headache days per month

≥8
headache days are migraine days

+

Headaches last

for >3 months

Focus on headache *days* vs migraine *attacks*

- Not all days need to be associated with migraine[2]
- Days when headaches were successfully treated with migraine-specific acute medications (eg, triptans) are also considered headache days[2]
- Ask about headache-*free* days if patient cannot recall number of actual headache days

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 optimising acute medication use/limiting medication overuse, addressing comorbid conditions, and adjusting patient lifestyles (eg, diet, exercise, eliminating caffeine consumption)[3,4]
- Treatment planning begins with a thorough history, which can include inquiry around these topics:

 Is the patient using more acute medications than recommended?	 Is the patient responding appropriately to acute medications?	 Is the patient meeting treatment goals?	 Has the patient followed the prescribed preventive regimen?	 Are there contraindications to some treatment options?

Revisit appropriate Chronic Migraine patients' management plans with BOTOX® treatment in mind

A history of preventive use[5]

Chronic migraine patients have tried 3.9 preventive treatments on average (n = 493)[5]

Identifying BOTOX® candidates (continued)

- As part of the evaluation, documenting symptoms for a Chronic Migraine diagnosis is important. When patients can understand the symptoms of their condition, they may feel less frustrated and more open to treatment options.

Headache frequency and duration	Evaluate both headache days and headache-free days
Headache severity	Ask about symptoms and intensity, which may shed light on headache severity[6]
Headache impact	Uncover how headache affects daily activities to avoid a patient minimising symptoms[6]
Migraine features	Discuss photophobia, phonophobia, pulsating quality, pain, aggravation with activity, headache location, nausea, and vomiting[7]

Greater disability correlates with headache frequency[8]

Patients with Chronic Migraine are significantly more likely to be severely disabled than those with episodic migraine (64.3% vs 43.2% Migraine Disability Assessment [MIDAS] grade IV).

PREEMPT Paradigm overview

- The PREEMPT Paradigm is based on approximately 10 years of study to assess patient type, muscle selection, dose, and treatment interval.[9-17]

155-195 UNITS	12 WEEKS	31-39 SITES
PROVEN DOSE	PROVEN SCHEDULE	PROVEN SITES
155 Units to 195 Units administered intramuscularly as 0.1 ml (5 Units) injections[1]	**Trial of 2 treatments, 12 weeks apart, with further re-treatment every 12 weeks[1*]**	**31-39 sites across 7 specific head and neck muscle areas[1]**

Summary of dose by area[1]

Muscle Area	Recommended dose/number of sites
Corrugator**	10 Units (2 sites)
Procerus	5 Units (1 site)
Frontalis**	20 Units (4 sites)
Temporalis**	40 Units (8 sites) FTP up to 50 Units (up to 10 sites)
Occipitalis**	30 Units (6 sites) FTP up to 40 Units (up to 8 sites)
Cervical paraspinal**	20 Units (4 sites)
Trapezius**	30 Units (6 sites) FTP up to 50 Units (up to 10 sites)
TOTAL DOSE	**155 Units to 195 Units (31 to 39 sites)**

***Re-treatment after 24 weeks should be determined per clinician's discretion.**
****Dose distributed bilaterally.**
FTP: follow-the-pain.

- The following section provides a step-by-step overview of the PREEMPT Paradigm for BOTOX®. Departures from the approved paradigm may lead to efficacy results and adverse events different from those seen in the clinical trials.

General injection considerations

Standard methods regardless of area

- For each injection, **the injection volume will be 0.1 mL** (equivalent to 5 Units)[1]
- **Consider injecting** in the most superficial aspect of the muscle
- **Evaluate the anatomy**, including relevant function and the effects of treatment on these muscles (eg, weakening)
- **Recognise unique anatomy**, as no two 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

- **Examine the patient** to identify unique anatomy and any muscle weakness or pain/tenderness
  - Visually **inspect** the muscle
  - Ask the patient to **activate** the muscle
  - **Palpate** the muscle
- **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
- Recommended needle: Sterile 30-gauge, 0.5 inch needle. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles.

During injection

- **Inject on 1 side first for bilateral injections**, then proceed to the other side and repeat at all the specified sites
- **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

FIGURE 1*

Example of procerus injection. Note the angle used to avoid the periosteum and target the muscle (Figure 1).

***This is a hypothetical patient.**

Anterior injections*

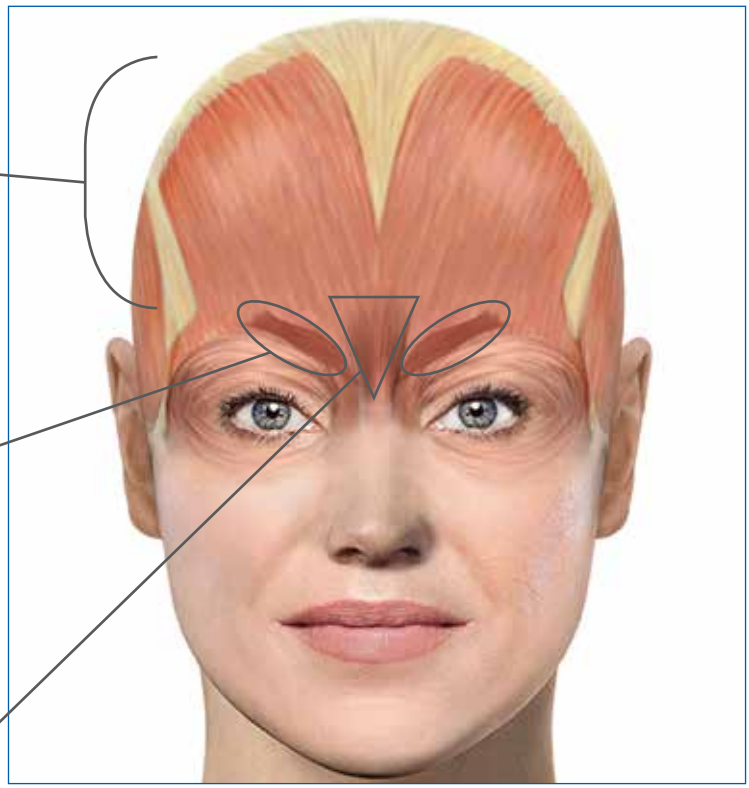
Anatomy of the face and head

- This section will highlight muscle area anatomy to provide additional context for the anterior injection sites.

Frontalis
Originates from the epicranial aponeurosis, and attaches distally to the skin of the forehead and eyebrow.[18]

Corrugator
Attaches to the nasal-frontal bone medially and the skin of the eyebrow laterally.[18,19]

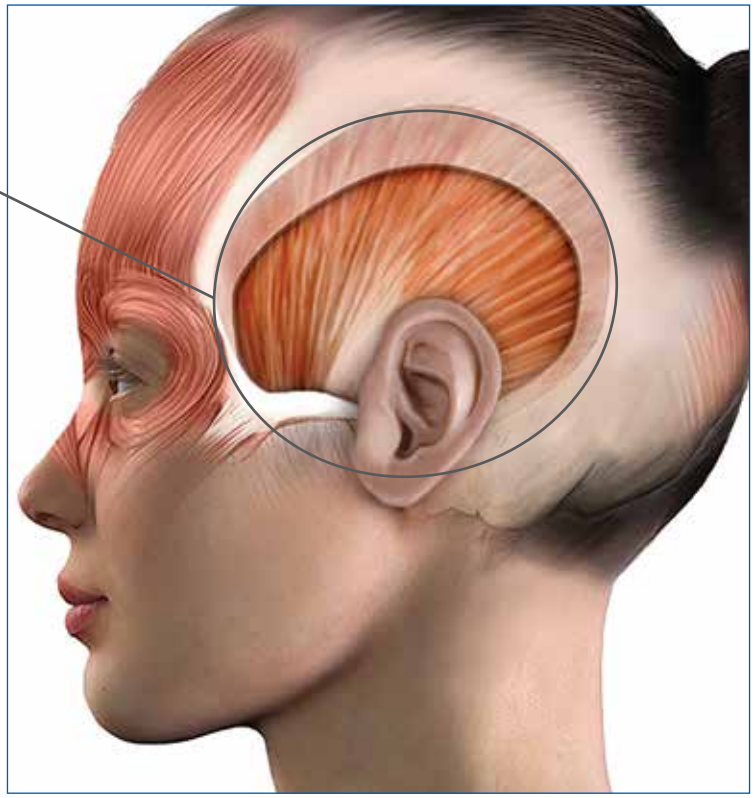
Procerus
Originates from the aponeurotic fascia of the nose and inserts into the glabellar skin.[18]



*Muscles and anatomical structures shown for anatomical reference only.

Temporalis

Originates from the temporal fossa and deep layer of the temporal fascia, and inserts into the top and medial surface of the coronoid process of the mandible.[18]



Interrelationship between muscles

- Corrugator muscle fibres and frontalis muscle fibres 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 fibres

Because of the close proximity of these muscles, pay close attention to the depth and angle of the needle. There can be a difference between the insertion point and where the medication is ultimately delivered.

Anterior injections* (continued)

Functional anatomy

- This section will highlight the functional anatomy of each anterior injection site, which may be important to consider when injecting.

The **frontalis muscle** is a brow elevator, pulling the brow upward.[18]

Weakening of this muscle may result in brow ptosis.

Activating the frontalis creates transverse lines on the forehead (Figure 2).[18]

FIGURE 2

The **corrugator muscle** is a brow depressor, pulling the brow downward.[18] Weakening of this muscle may elevate the brow.

Activating the corrugator creates vertical lines between the brow (Figure 3).[18]

FIGURE 3

*Muscles and anatomical structures shown for anatomical reference only.

†This is a hypothetical patient.

The **procerus muscle** draws down the medial aspect of the brow.[18]

Activating the procerus creates a transverse ridge over the nose (Figure 4).[18]

FIGURE 4†

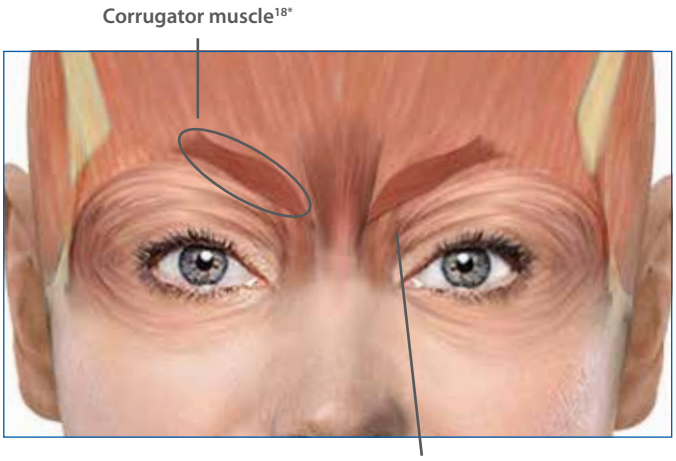
The **temporalis** is a masticatory muscle. Clenching the teeth activates the temporalis and can help localise the muscle (Figure 5).[18]

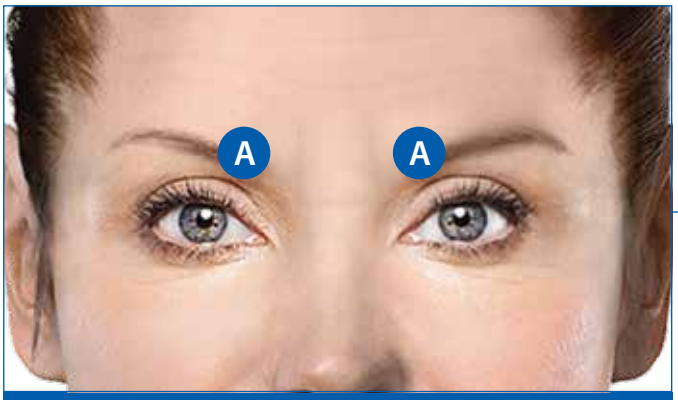
FIGURE 5

Fixed-site, fixed-dose corrugator PREEMPT protocol*

Dose[1]

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





Corrugator injection sites

A

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

*Muscles and anatomical structures shown for anatomical reference only.

FIGURE 6

Additional factors to consider prior to injection

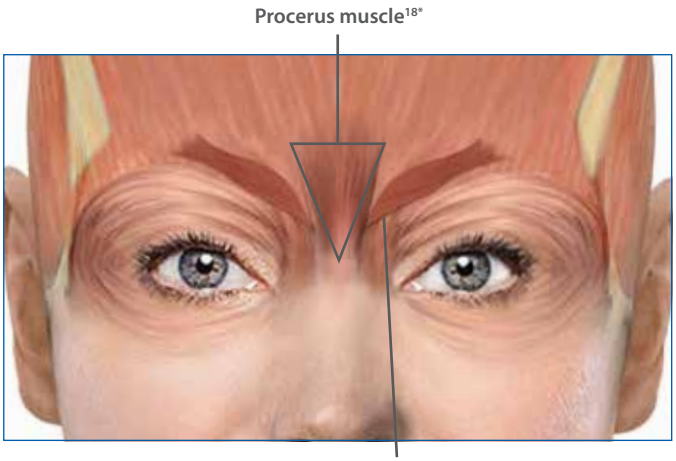
- Ask the patient to furrow the brow, which activates the corrugator and causes medial and inferior movement of the brow
- Palpate and pinch the muscle, holding between the thumb and index finger (Figure 6)
- Consider injecting at a 90º angle into the belly of the muscle, remaining above the periosteum, to help ensure medication delivery into the corrugator and not into a nearby muscle (Figure 6)
- 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

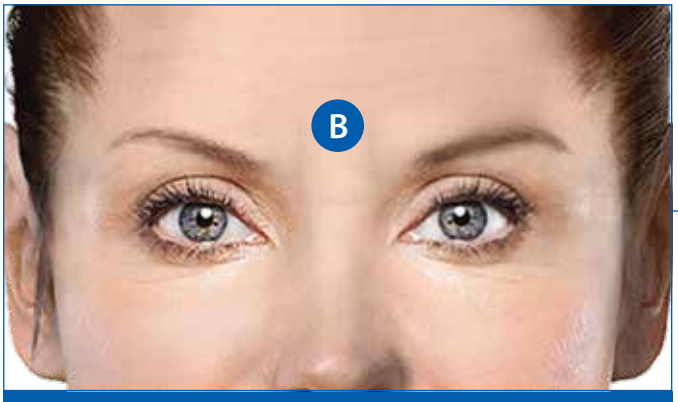
Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

Fixed-site, fixed-dose procerus PREEMPT protocol*

Dose[1]

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





Procerus injection site

B

Injection site

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

*Muscles and anatomical structures shown for anatomical reference only.

FIGURE 7

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 90º to deliver medication into the procerus and not a nearby muscle (eg, frontalis) (Figure 7)
- 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

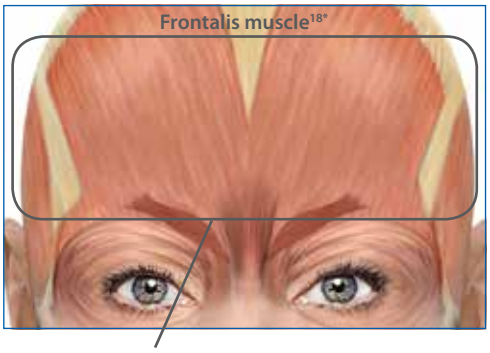
Be cautious of the thin muscles of the forehead and brow. Stay in the most superficial aspect of the muscle to avoid hitting the periosteum.

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

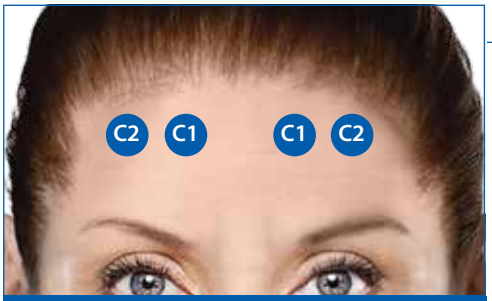
Fixed-site, fixed-dose frontalis PREEMPT protocol*

Dose[1]

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



Medial inferior edge of the superior orbital rim[19*]



Frontalis injection sites

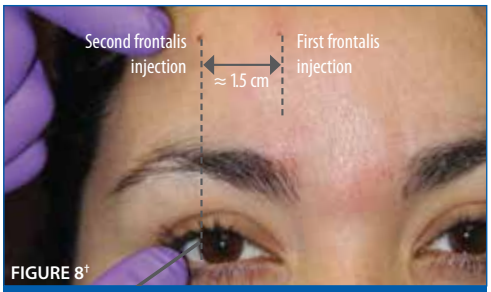


FIGURE 8[†]

Lateral limbus of the cornea[18*]

C1

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

C2

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 8). This may vary based on individual anatomy

*Muscles and anatomical structures shown for anatomical reference only.

†This is a hypothetical patient.

FIGURE 9

Additional factors to consider prior to injection

- Angle the needle superiorly at 45º (Figure 9)
- 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 32)
- Consider that injection points are different than medication delivery points
- If patients are concerned about discomfort, the injector may consider a topical anaesthetic in this area

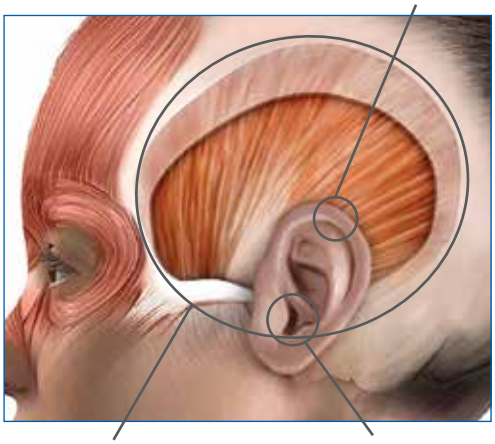
Account for individual anatomy. Forehead sizes are different, so generally stay within the upper one-third of the forehead.

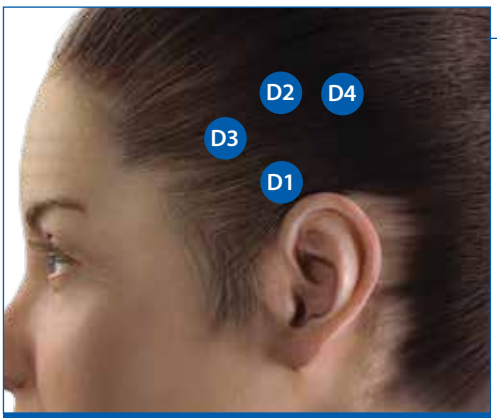
Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

Fixed-site, fixed-dose temporalis PREEMPT protocol*

Dose[1]

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





Temporalis injection sites

D1

Injection site

- Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm (~2 fingerbreadths)

D2

Injection site

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

D3

Injection site

- Move about 1.5 cm (~1 fingerbreadth) forward, toward the face, from the first and second injections. Make the third injection halfway vertically between injection sites 1 and 2

D4

Injection site

- Move about 1.5 cm (~1 fingerbreadth) back from the second injection, and in line with the midportion (helix) of the ear

*Muscles and anatomical structures shown for anatomical reference only.

FIGURE 10

Additional factors to consider prior to injection

- Inject the most superficial aspect of the muscle at 45º (Figure 10)
- 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 10)
- Clenching the teeth activates the temporalis and can help localise 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

Follow-the-pain temporalis PREEMPT protocol*

Dose[1]

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

Injection site[1,20]

- Up to an additional 2 doses in either the right or left temporalis muscle, at the points of greatest pain or tenderness.

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

Posterior injections*

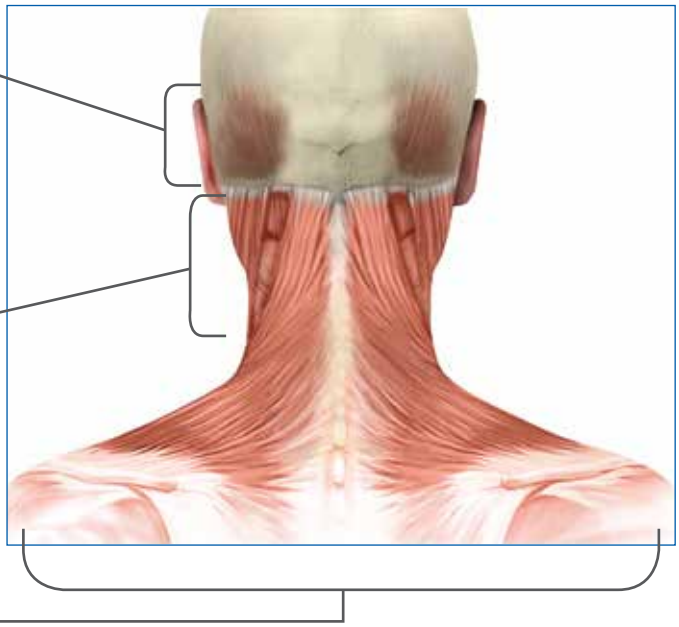
Muscles of the neck and posterior head

- This section will highlight muscle area and functional anatomy for each posterior injection site, which may be important to consider when injecting.

Occipitalis
Originates at the highest nuchal line and inserts into the epicranial aponeurosis, which is attached to the frontalis.[18]

Cervical paraspinal
muscles should be considered a group (including the splenius capitis and semispinalis capitis) running deep alongside the cervical spine.[18]

Trapezius
Trapezius – A flat, triangular muscle situated over the back of the neck and upper thorax.[18]



*Muscles and anatomical structures shown for anatomical reference only.

Functional anatomy

- One function of the occipitalis is as an anchor for the frontalis.[18]
- Cervical paraspinal muscles stabilise and allow for movement of the head and cervical spine (Figure 11).[18]
- In addition to the muscles that are deep to the trapezius, the trapezius functions to stabilise and bend the head and neck backward and laterally (Figure 12).[18]

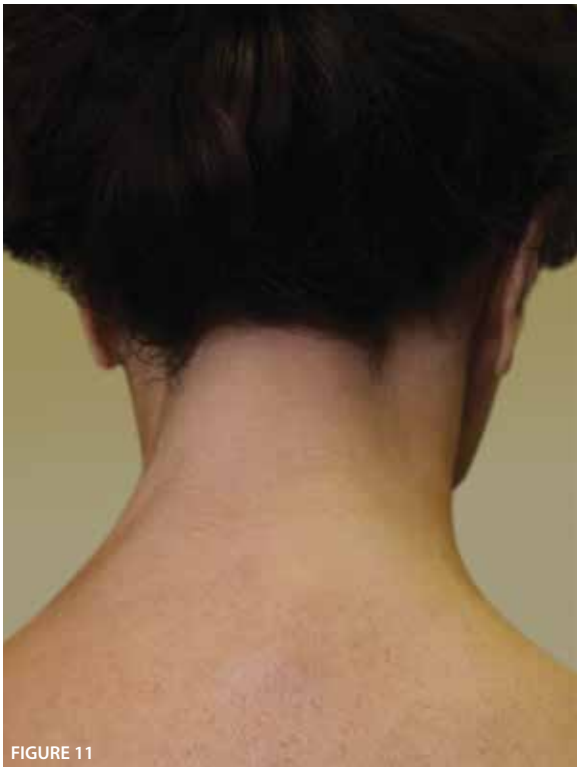


FIGURE 11

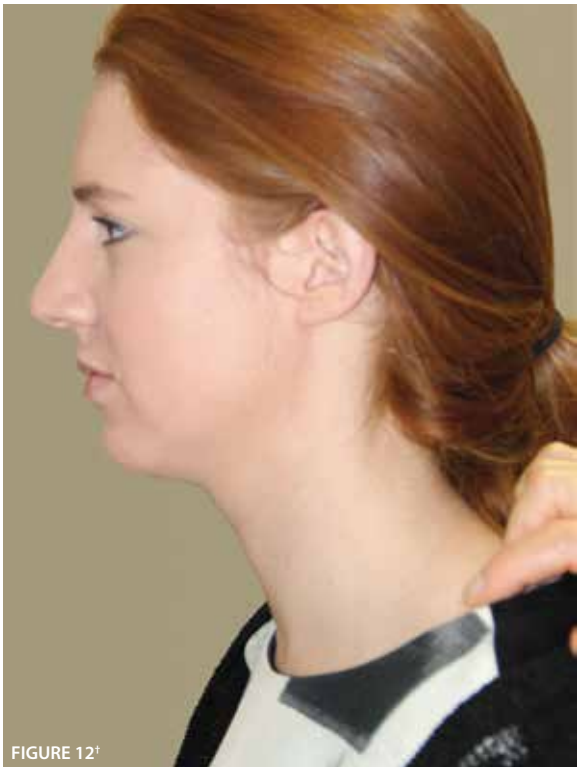


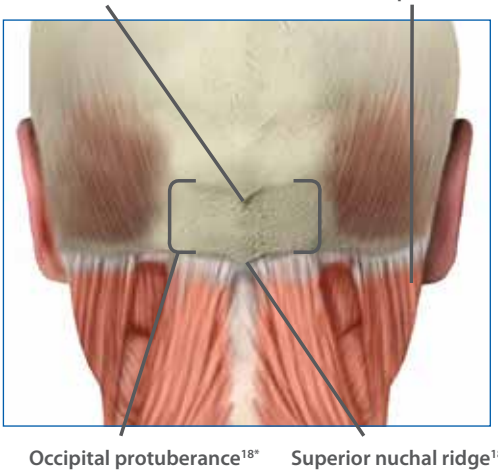
FIGURE 12[†]

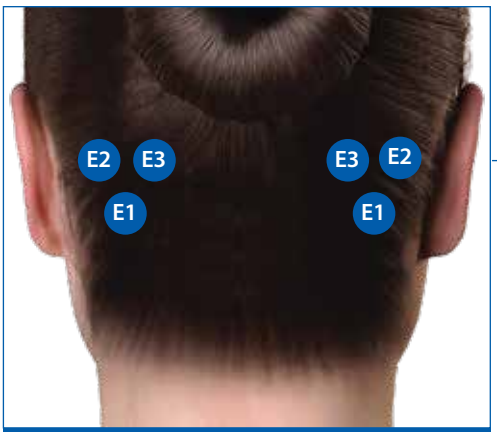
[†]This is a hypothetical patient.

Fixed-site, fixed-dose occipitalis PREEMPT protocol*

Dose[1]

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





Occipitalis injection sites

*Muscles and anatomical structures shown for anatomical reference only.

E1

Injection site

- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 13, page 25)
- Locate the tip of the mastoid process behind the ear (Figure 13, page 25)
- 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

E2

Injection site

- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 20) for the second muscle area for injection (eg, at the 10 o'clock position for the left injection)

E3

Injection site

- 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)

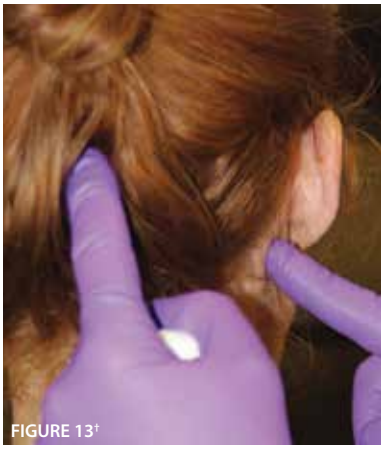


FIGURE 13†

FIGURE 14†

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 14)
- Inject at 45°, angling the needle upward and away from the neck (Figure 14)
- Injecting too low in the neck may result in neck pain and weakness; inject above the nuchal ridge

Follow-the-pain occipitalis PREEMPT protocol*

Dose[1]

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

Injection site[1,20]

- Up to an additional 2 doses in either the right or left occipitalis muscle, at the points of greatest pain or tenderness

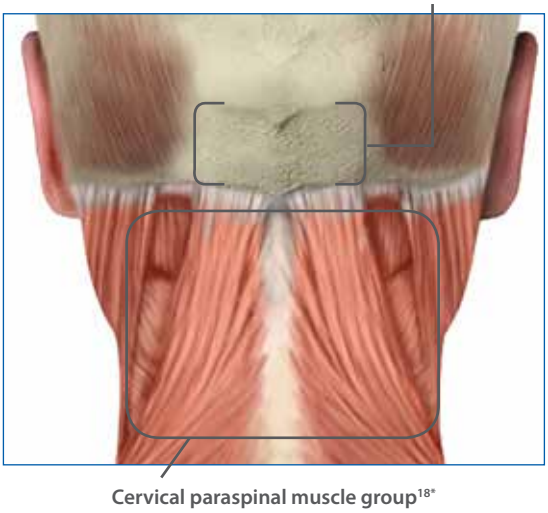
Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

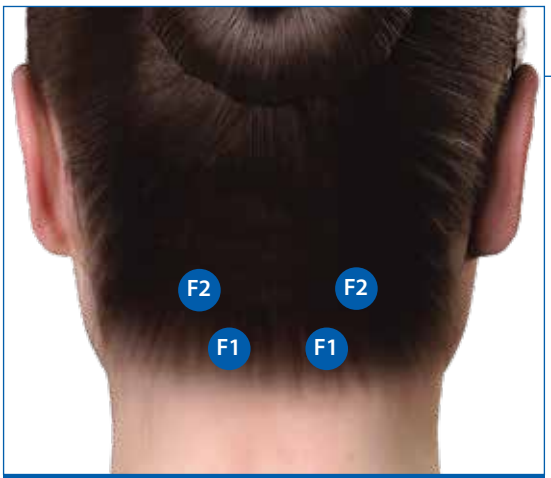
†This is a hypothetical patient.

Fixed-site, fixed-dose cervical paraspinal PREEMPT protocol*

Dose[1]

- 5 Units (0.1 mL) in each site
- Total 20 Units divided into 4 sites (2 on each side)





Cervical paraspinal injection sites

F1

Injection site

- 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

F2

Injection site

- Measure about 1.5 cm (~1 fingerbreadth) diagonally up at a 45° angle toward the helix of the ear (see diagram on page 20) from the first injection site

*Muscles and anatomical structures shown for anatomical reference only.

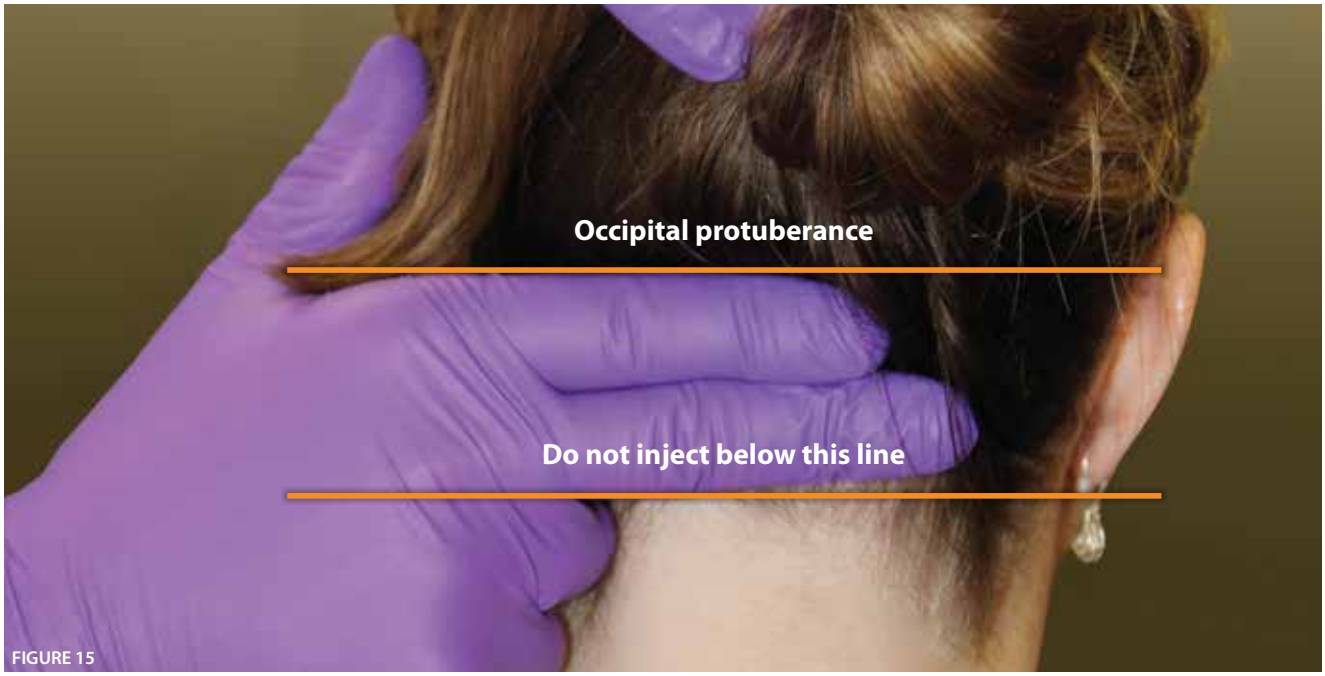


FIGURE 15

Additional factors to consider prior to injection

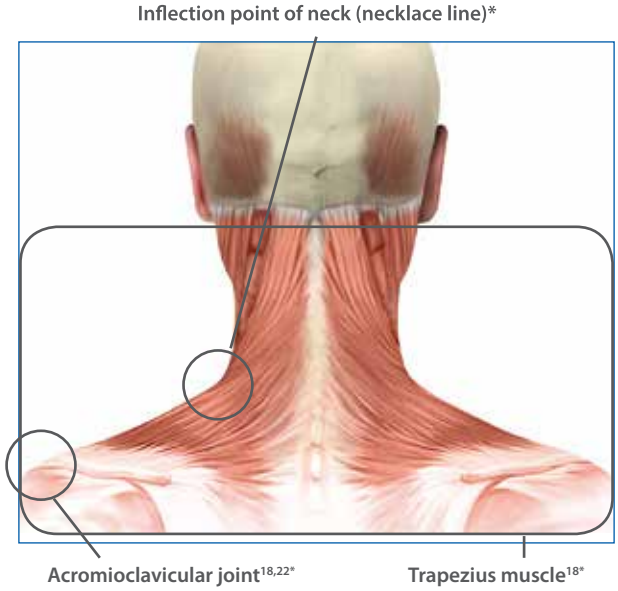
- Assess patient for preexisting neck pain/weakness to help properly set expectations about this muscle group
- Position the patient upright, with the head in a neutral position; flexing far forward may result in injecting too deep
- Visualise a line across the neck, ~2 fingerbreadths down from the occipital protuberance, and avoid injecting below that line (Figure 15)
- Inject higher (in the hairline) to help minimise the potential for neck weakness – consider the area the suboccipitalis region
- Inject in the most superficial aspect of the muscle, angling 45° 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 22 for details)

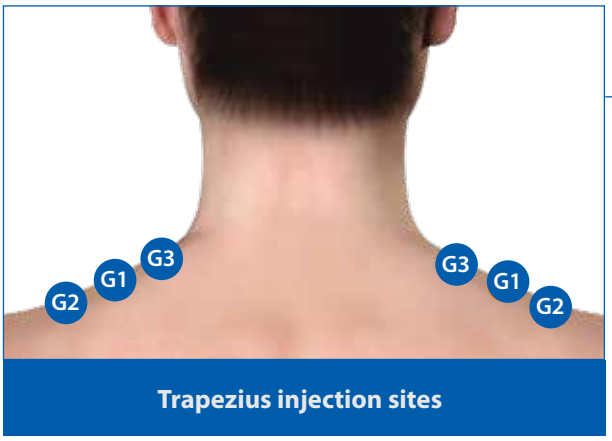
Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

Fixed-site, fixed-dose trapezius PREEMPT protocol*

Dose[1]

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





Trapezius injection sites

G1

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

G2

Injection site

- Split the difference between injection 1 and the acromioclavicular joint

G3

Injection site

- Split the difference between injection 1 and the necklace line

*Muscles and anatomical structures shown for anatomical reference only.

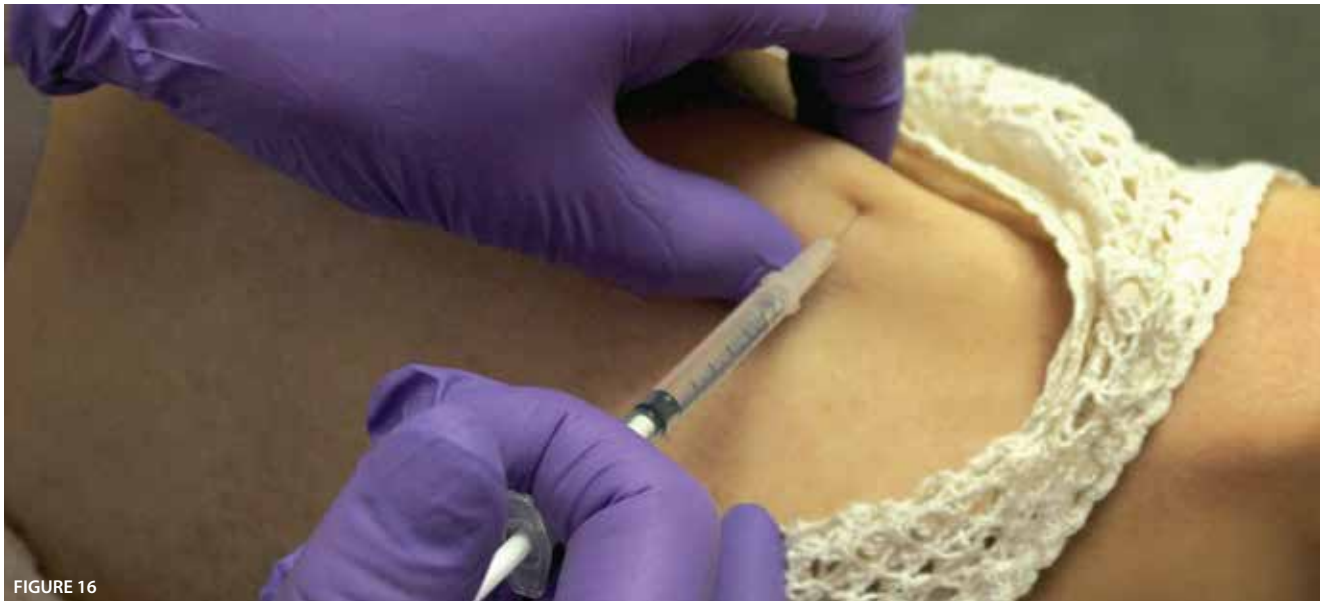
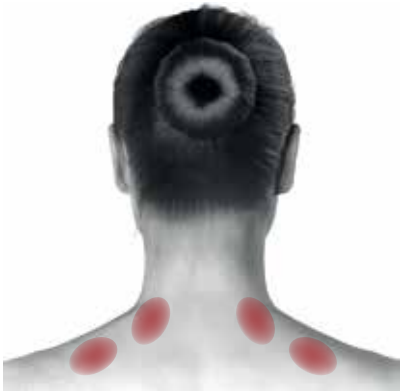


FIGURE 16

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 16)
- Inject the supraclavicular portion of the muscle, lateral to the neckline and medial to the deltoid/ acromioclavicular joint (Figure 16)
- 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

Follow-the-pain trapezius PREEMPT protocol*



Dose[1]

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

Injection site[1,20]

- Up to an additional 4 doses in either the right or left trapezius muscle, at the points of greatest pain or tenderness

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

Common adverse events associated with the use of BOTOX® for chronic migraine[1]

System organ class	Common (1-10 per 100 patients)
Nervous system disorders	Headache, migraine, facial paresis
Eye disorders	Eyelid ptosis
Skin and subcutaneous tissue disorders	Pruritus, rash
Musculoskeletal and connective tissue disorders	Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness
General disorders and administration site conditions	Injection site pain

Discontinuation rates due to adverse events[1,9]

- Pooled analysis (pooled data and double-blind phase data) of the 24-week double-blind PREEMPT study[1,9]

3.8% BOTOX®

vs

1.2% Placebo

Patient assessment before injection*

- 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 counselling will help set patient expectations. Patients with preexisting conditions should be carefully assessed to determine if they are appropriate for injection.

Patient examination:

- ✓ VISUALLY INSPECT THE MUSCLE
- ✓ ASK THE PATIENT TO ACTIVATE THE MUSCLE
- ✓ PALPATE THE MUSCLE

Preexamination of the brow

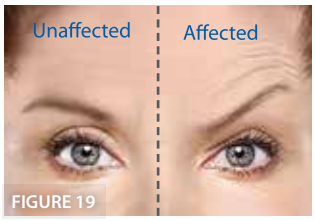
- **What to look for:** Inspect for excessive soft tissue resting near the upper lid of the eye and lid drooping (Figure 17).

FIGURE 17†

Preexamination of the brow (continued)

- Ptosis may be a preexisting condition or may occur after BOTOX® treatment. Patients should be evaluated for both eyelid and eyebrow ptosis.[20]

Lid ptosis
Notice the asymmetry as a result of the drooping lid on the right.[21*]



Medial brow ptosis
Notice the medial brow depression and lateral brow elevation on the right.*

Pseudoptosis
Notice the extra soft tissue around the eyelid and the misalignment of the lids.[21*]

Full brow ptosis
Notice how the weakened frontalis muscle has depressed both the medial and lateral brow.*

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 her eyebrows (Figure 22). Observe the dynamic muscle activity and whether there is any compensatory mechanism keeping the eyelids open in the presence of brow weakness.

*Muscles and anatomical structures shown for anatomical reference only.

†This is a hypothetical patient.

Patient assessment before injection*

Preexamination of the neck

- **What to look for:** Neck pain and neck weakness may be present among Chronic Migraine patients.[22] Inspect the patient for a head-forward position, which may indicate preexisting muscle weakness (Figure 23).

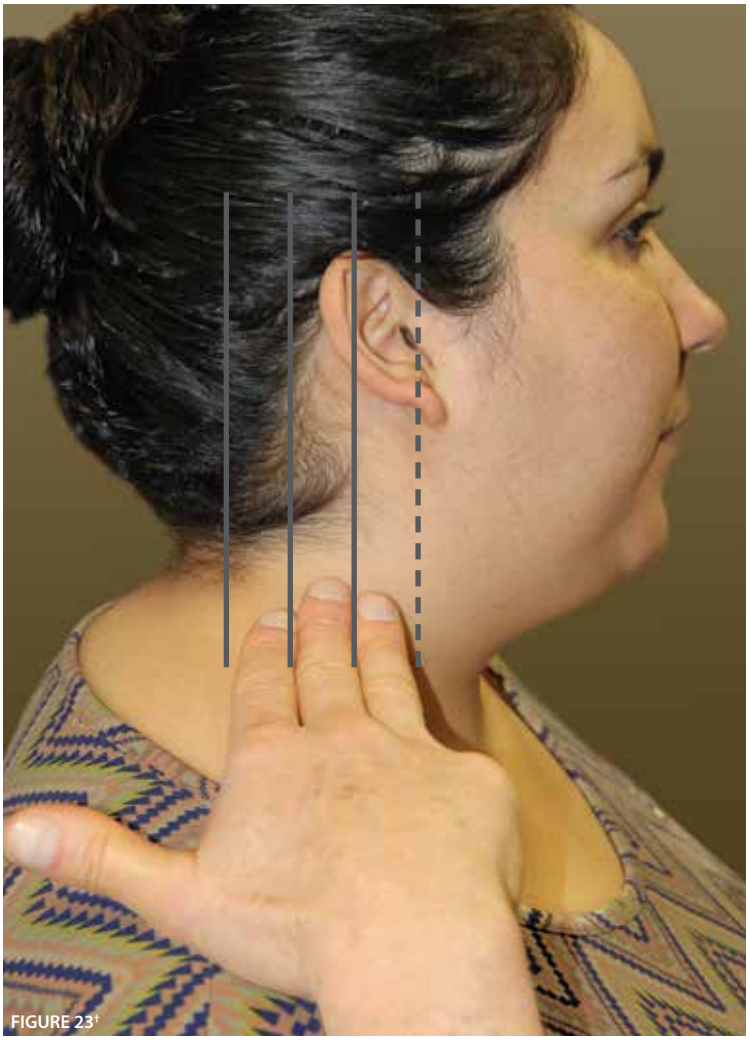


FIGURE 23†

Three-fingerbreadths', head-forward position

- **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 centre of gravity (Figure 24). If the tragus is anterior to this line by 2 to 3 fingerbreadths, this may be abnormal (Figure 23).

Prior to BOTOX® injections, consider preexamining patients for pain sensitivity in the neck.

FIGURE 24†

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

Notes

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References

1. BOTOX® Israeli Product Information, February 2021.
2. Lipton RB. *Headache*. 2011; 51 (suppl 2): 77S–83S.
3. Dodick DW. *N Engl J Med*. 2006; 354(2): 158–165.
4. Silberstein SD. *Neurology*. 2000; 55(6): 754–762.
5. Blumenfeld AM, et al. *Headache*. 2013; 53(4): 644–655.
6. Holmes WF, et al. *Headache*. 2001; 41(4): 343–350.
7. Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013; 33(9): 629–808.
8. Bigal ME, et al. *Headache*. 2003; 43(4): 336–342.
9. Dodick DW, et al. *Headache*. 2010; 50(6): 921–936.
10. Blumenfeld A, et al. *Headache*. 2010; 50(9): 1406–1418.
11. Binder WJ, et al. *Otolaryngol Head Neck Surg*. 2000; 123(6): 669–676.
12. Elkind AH, et al. *J Pain*. 2006; 7(10): 688–696.
13. Saper JR, et al. *Pain Med*. 2007; 8(6): 478–485.
14. Relja M, et al. *Cephalalgia*. 2007; 27(6): 492–503.
15. Aurora SK, et al. *Headache*. 2007; 47(4): 486–499.
16. Silberstein SD, et al. *Mayo Clin Proc*. 2005; 80(9): 1126–1137.
17. Mathew NT, et al. *Headache*. 2005; 45(4): 293–307.
18. Standring S, ed. Gray's Anatomy: The Anatomical Basis of Clinical Practice. 40th ed. London, England: Churchill Livingstone; 2008.
19. Miloro M, et al. Peterson's Principles of Oral and Maxillofacial Surgery. 3rd ed. Shelton, CT: People's Medical Publishing-USA; 2011.
20. Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Brin MF, Binder WJ (2017) Insights into the functional anatomy behind the PREEMPT injection paradigm: guidance on achieving optimal outcomes. Headache 57:766–777
21. Stedman's Medical Dictionary. 28th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006.
22. Calhoun AH, et al. *Headache*. 2010; 50(8): 1273–1277.

BOTOX® 50/ BOTOX® 100/ BOTOX® 200

Indication: Botox is indicated for Symptom relief in adults fulfilling criteria for chronic migraine (headaches on ≥15 days per month of which at least 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications
Contraindications: known hypersensitivity to botulinum toxin type A or to any of the excipients (human albumin, Sodium chloride), presence of infection at the proposed injection site(s).

Safety information
Special Population: Elderly patients with significant medical history and concomitant medications should be treated with caution.
Special warnings and precautions: Botox should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Lambert-Eaton Syndrome in patients with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders.
Interactions: 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.
Pregnancy, lactation and fertility: Botox should not be used during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. The use of Botox during lactation cannot be recommended. Studies in male and female rats have shown fertility reductions.
Effects on ability to drive and use machines: Botox may cause asthenia, muscle weakness, dizziness and visual disturbance, which could affect driving and using machines.
Undesirable effects: In general, adverse reactions occur within the first few days following injection and, while generally transient, may have a 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 and/or muscles remote from the site of injection has been reported. As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised 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. Fever and flu syndrome have also been reported after injections of botulinum toxin.

* For full information please see Botox® prescribing information

Full prescribing information can be received from Allergan - Abbvie Biopharmaceutical Ltd., Israel, at 4 Hacharash Street, Hod Hasharon, 4524075. Tel: 09-7909600, Fax: 09-7909606.