abbvie

**BOTOX®**

**(Botulinum Toxin Type A)**

**Purified Neurotoxin Complex**

## Description:

**BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuum-dried form of purified botulinum toxin type A, produced from a culture of the Hall strain of ***Clostridium botulinum*** grown in a medium containing N-Z amine and yeast extract. It is purified from the culture solution by a series of acid precipitation to a crystalline complex consisting of the active high molecular weight toxin protein and an associated hemagglutinin protein. The crystalline complex is re-dissolved in a solution containing saline and albumin and sterile filtered (0.2 microns) prior to vacuum-drying. **BOTOX®** is to be reconstituted with sterile, non-preserved saline prior to intramuscular injection.

## Active Ingredient:

Each vial of **BOTOX®** Purified Neurotoxin Complex contains either 50 units (U), 100 units (U) or 200 units (U) of ***Clostridium Botulinum*** toxin type A, in a sterile, vacuum-dried form without preservative. One unit (U) corresponds to the calculated median lethal intraperitoneal dose (LD/50) in mice of the reconstituted **BOTOX®** injected.

## Excipients:

Human albumin: 0.25mg for 50 Units; 0.5 mg for 100 Units or 1.0 mg for 200 Units
Sodium chloride: 0.45 mg for 50 Units; 0.9 mg for 100 Units or 1.8 mg for 200 Units

## Indications

### Glabellar Lines

**BOTOX®** is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients below 65 years of age.

### Lateral Canthal Lines

**BOTOX®** is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.

### Forehead Lines

**BOTOX®** is indicated for the temporary improvement in the appearance of moderate to severe forehead lines associated with frontalis muscle activity in adult patients.

**Strabismus and Blepharospasm**

**BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

The efficacy of **BOTOX®** Purified Neurotoxin Complex in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful, or multiple injection over time may be required. **BOTOX®** is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair.

**Dosage and Administration**

The use of **BOTOX®** should only be prescribed by a specialist and it should only be used under the supervision of a specialist.

***Glabellar Lines***

**BOTOX®** is reconstituted with 0.9% sterile, non-preserved saline (50 Units in 1.25 mL or 100 Units in 2.5 mL to be injected as 4 Units/0.1 mL). Reconstituted BOTOX® 0.1 mL is administered using a 30 gauge needle in each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units.

In controlled clinical trials, improvement of severity of glabellar lines generally occurred within one week after treatment. Typically, the initial doses of reconstituted **BOTOX®** induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

Injection intervals should be no more frequent than every 3 months and should be performed using the lowest effective dose.

The duration of effect of **BOTOX®** for glabellar lines is approximately 3-4 months in most patients. In some patients, the duration of effect has been reported up to 6 months. The safety and effectiveness of more frequent dosing with **BOTOX®** has not been clinically evaluated and is not recommended.

*Glabellar Lines Injection Technique:*

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected.

In order to reduce the complication of ptosis the following steps should be taken:

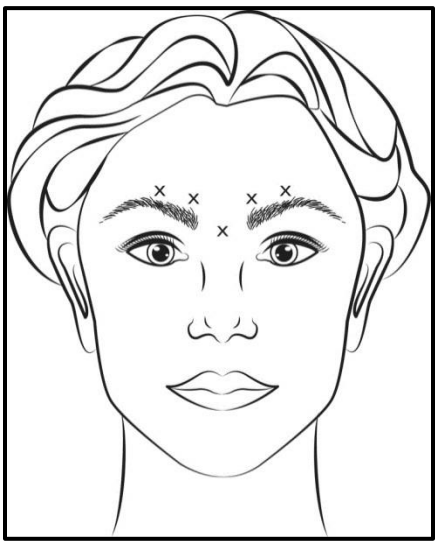
• Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.

• Medial corrugator injections should be placed at least 1 centimeter above the bony supraorbital ridge.

• Ensure the injected volume/dose is accurate and where feasible kept to a minimum.

• Do not inject toxin closer than 1 cm above the central eyebrow.

**Figure 1**



***Lateral Canthal Lines***

Using a 30-33 gauge needle (preferably a tuberculin syringe), draw at least 0.6 mL of reconstituted BOTOX® and inject 4 Units/0.1 mL of reconstituted BOTOX® into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side).

*Lateral Canthal Lines Injection Technique:*
Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients.

Injections should be given with the needle bevel tip up and oriented away from the eye.

The first injection (A) should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow's feet region are above and below the lateral canthus, inject per Figure 2. Alternatively, if the lines in the crow's feet region are primarily below the lateral canthus, inject per Figure 3.

**Figure 2:**

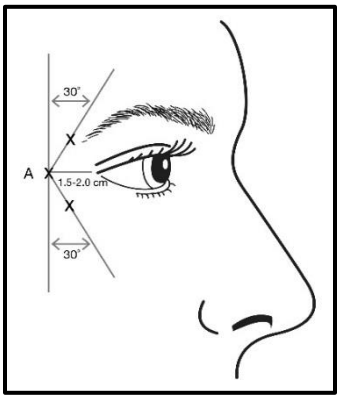
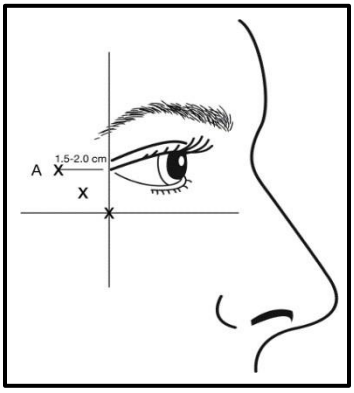



**Figure 3:**




In order to reduce the risk of eyelid ptosis, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

The treatment with BOTOX® should be given not more than three cycles and the injections given in each cycle are not more than 24 units.

For simultaneous treatment with glabellar lines, the dose is 24 Units for lateral canthal lines and 20 Units for glabellar lines (see Glabellar Lines Administration and Figure 1), with a total dose of 44 Units.

***Forehead Lines***

Using a 30 gauge needle, inject 4 Units/0.1 mL of reconstituted BOTOX® into 5 sites in the frontalis muscle, for a total dose of 20 Units/0.5 mL (see Figure 4 below).

It is recommended to treat forehead lines in conjunction with glabellar lines to minimize the potential for brow ptosis. The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units/1.0 mL.

The time to retreatment of BOTOX® for forehead lines is approximately 4 months. The safety and effectiveness of dosing with BOTOX® more frequently than every 3 months have not been clinically evaluated.

When identifying the location of the appropriate injection sites in the frontalis muscle, assess the overall relationship between the size of the patient's forehead, and the distribution of frontalis muscle activity.

Locate the following horizontal treatment rows by light palpation of the forehead at rest and maximum eyebrow elevation:

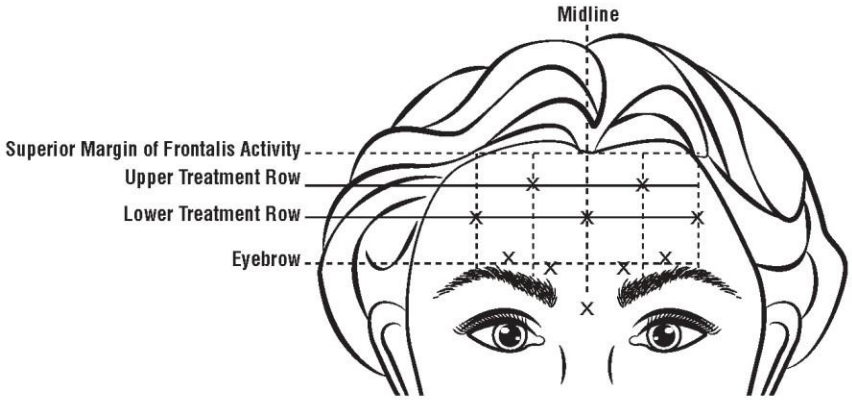
- Superior Margin of Frontalis Activity: approximately 1 cm above the most superior forehead crease
- Lower Treatment Row: midway between the superior margin of frontalis activity and the eyebrow, at least 2 cm above the eyebrow

- Upper Treatment Row: midway between the superior margin of frontalis activity and lower treatment row

Place the 5 injections at the intersection of the horizontal treatment rows with the following vertical landmarks:

- On the lower treatment row at the midline of the face, and 0.5 – 1.5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side.
- On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side.

**Figure 4:**




Improvement in the severity of forehead lines seen at maximum eyebrow elevation occurred within one week of treatment.

For simultaneous treatment with glabellar lines and lateral canthal lines, the total dose is 64 Units, comprising of 20 Units for forehead lines, 20 Units for glabellar lines, and 24 Units for lateral canthal lines.

The safety and effectiveness of dosing with **BOTOX®** more frequently than every 3 months have not been clinically evaluated.

***Strabismus***

**BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex is intended for injection into the extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

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

To prepare the eye for **BOTOX®** injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

***Note:*** The volume of **BOTOX®** injected for treatment of strabismus should be between 0.05 mL to 0.15 mL, per muscle.

*Strabismus Dosage:* The initial listed doses of the diluted **BOTOX®** Purified Neurotoxin Complex (see Dilution Table below) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Over corrections lasting over 6 months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

I. Initial doses in units (abbreviated as U). Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
   A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 U to 2.5 U in any one muscle.
   B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 U to 5.0 U in any one muscle
   C. For persistent VI nerve palsy of one month or longer duration: 1.25 U to 2.5 U in the medial rectus muscle

II. Subsequent doses for residual or recurrent strabismus.
   A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose
   B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose
   C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to twice the size of the previously administered dose
   D. Subsequent injections should not be administered until the effect of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles
   E. The maximum recommended dose as a single injection for any muscle is 25 U

***Blepharospasm***

For blepharospasm, diluted **BOTOX®** Purified Neurotoxin Complex (see Dilution Table) is injected using sterile, 27-30 gauge needle with or without electromyographic guidance. 1.25 U to 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid is the initial recommended dose. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However there appears to be little benefit obtainable from injecting more than 5.0 U per site. Some tolerance may be found when **BOTOX®** is used in treating blepharospasm if treatments are given any more frequently than every three months, and it is rare to have the effect be permanent. The cumulative dose of BOTOX treatment for blepharospasm in a 30-day period should not exceed 200 Units.

## Contraindications

**BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex is contraindicated in individuals with known hypersensitivity to any ingredient in the formulation and in the presence of infection at the proposed injection site(s).

## Warnings

Do not exceed the recommended dosage and frequency of administration of **BOTOX®**. Risks resulting from administration at higher dosages are not known.

Caution should be exercised when BOTOX® is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle.

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

Caution should be exercised when administering **BOTOX®** to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX®**. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown

extreme sensitivity to the systemic effects of typical clinical doses. In some of the cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

There have been reports following administration of **BOTOX®** for other indications of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

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. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

**Precautions**

***General:*** The safe and effective use of **BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX®** must understand the relevant neuromuscular and orbital anatomy and any alterations to the anatomy due to prior surgical procedures, and standard electromyographic techniques.

As with all biologic products, epinephrine and other precautions as necessary should be available should an anaphylactic reaction occur.

During the administration of **BOTOX®** Purified Neurotoxin Complex for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available.

Reduced blinking from **BOTOX®** Purified Neurotoxin Complex injection of the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means. Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles.

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Caution should be used when **BOTOX®** treatment is used in patients who have an inflammatory skin problem at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart as these patients were excluded from the Phase 3 safety and efficacy trials.

Injection intervals of **BOTOX®** should be no more frequent than every three months and should be performed using the lowest effective dose (see Adverse Reactions, Immunogenicity)

**Hypersensitivity Reactions**

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX® inappropriately diluted with 5 ml of 1% lidocaine. The causal role of BOTOX®, lidocaine, or both cannot be reliably determined

**Adverse Effects Distant from the Site of Injection**

Post-marketing safety data from Botox® and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms that are consistent with the mechanism of action of botulinum toxin have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in patients who have underlying conditions and comorbidities that would predispose them to these symptoms including adults treated for spasticity and other conditions, and are treated with high doses. Swallowing and breathing difficulties can be life threatening and death has been reported, although a definitive causal association to BOTOX® has not been established.

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

**Seizures**

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

**Immunogenicity**

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX® treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

***Information for Patients***

Patients with blepharospasm may have been extremely sedentary for a long time. Sedentary patients should be cautioned to resume activity slowly and carefully following the administration of **BOTOX®** Purified Neurotoxin Complex.

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

***Drug Interactions***

The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or any other drugs that interfere with neuromuscular transmission. Caution should be exercised when **BOTOX®** Purified Neurotoxin Complex is used in patients taking any of these drugs. (See Warnings).

Co-administration of **BOTOX®** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes 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.

***Pregnancy***

Administration of **BOTOX®** is not recommended during pregnancy. There are no adequate and well-controlled studies of **BOTOX®** in pregnant women. When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of **BOTOX®** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification.

In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 to 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX®**.

If the patient becomes pregnant after the administration of this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations that have been observed in rabbits.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***
Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX®**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and testicular atrophy or an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos.

***Nursing Mothers***
It is not known whether this drug is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when **BOTOX®** Purified Neurotoxin Complex is administered to a nursing woman. The use of BOTOX® during lactation is not recommended.

***Pediatric Use***
Safety and effectiveness in children below the age of 12 has not been established.

Safety and efficacy of **BOTOX®** have not been established for patients below the age of 18 years for glabellar lines, lateral canthal lines and forehead lines.

***Geriatric Use***
***Generally,*** clinical studies of **BOTOX®** did not identify differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased cardiac function and of concomitant disease or other drug therapy.

*Lateral Canthal Lines*
In the two lateral canthal lines clinical studies of **BOTOX®**, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

## Adverse Reactions

### *General*

The most serious adverse events reported for other indications studied include rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with botulinum toxin. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease (See Warnings). The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, a report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

There have been reports of seven cases of diffuse skin rash and two cases of local swelling of the eyelid skin lasting for several days following eyelid injection.

### *Strabismus*

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms. Extraocular muscles adjacent to the injection site are often affected, causing ptosis or vertical deviation, especially with higher doses of **BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex. The incidence rates of these side effects in 2058 adults who received 3650 injections for horizontal strabismus are listed below:

**Eye disorders**

| | |
|---|---|
| Very common: | Eyelid ptosis, vertical deviation, eye movement disorder |
| Uncommon: | Ocular retrobulbar hemorrhages, eye penetration, Holmes-Adie pupil |
| Rare: | Vitreous hemorrhage |

The incidence of ptosis was much less after inferior rectus injection (0.9 %) and much greater after superior rectus injection (37.7%). The incidence rates of these side effects persisting for over 6 months in enlarged series of 5587 injections of horizontal muscles in 3104 patients are listed below:

| | |
|---|---|
| Ptosis lasting over 180 days | 0.3% |
| Vertical deviation greater than 2 prism diopters lasting over 180 days | 2.1% |

In these patients the injection procedure itself caused 9 scleral perforations. A vitreous hemorrhage occurred and later cleared in one case. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar hemorrhages occurred. Decompression of the orbit after 5 minutes was done

to restore retinal circulation in one case. No eye lost vision from retrobulbar hemorrhage. Five eyes had papillary change consistent with ciliary ganglion damage (Adies pupil).

***Blepharospasm***

In 1684 patients who received 4258 treatments (involving multiple injections) for blepharospasm, the incidence rates of adverse reactions per treated eye are listed below:

| | |
|---|---|
| **Nervous system disorders** | |
| Uncommon: | Dizziness, facial palsy |
| **Eye disorders** | |
| Very common: | Eyelid ptosis, Vertical deviation |
| Common: | Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, lacrimation increase |
| Uncommon: | Keratitis, ectropion, diplopia, entropion, vision blurred |
| Rare: | Eyelid edema |
| Very rare | Ulcerative keratitis, corneal epithelium defect, corneal perforation |
| **Skin and subcutaneous tissue disorder** | |
| Common: | Ecchymosis |
| Uncommon: | Rash |
| **General disorders and administration site conditions** | |
| Uncommon: | Fatigue |

Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

In two cases of VII nerve disorder (one case of an aphakic eye) reduced blinking from **BOTOX®** Purified Neurotoxin Complex injection of the orbicularis muscles led to serious corneal exposure, persistent epithelial defect and corneal ulceration. Perforation requiring corneal grafting occurred in one case, an aphakic eye. Avoidance of injection into the lower lid area to avoid ectropion may reduce this hazard. Vigorous treatment of any corneal epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Two patients previously incapacitated by blepharospasm experienced cardiac collapse attributed to over-exertion within three weeks following **BOTOX®** Purified Neurotoxin Complex therapy. Sedentary patients should be cautioned to resume activity slowly and carefully following the administration of **BOTOX®**

***Glabellar Lines***

In clinical trials of **BOTOX®** the most frequently reported adverse events following injection of **BOTOX®** were headache, respiratory infection, flu syndrome, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events were generally transient but may last several months.

The data described in the table below reflects exposure to **BOTOX®** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX®** in the improvement of the appearance of glabellar lines (see clinical studies). Adverse events of any cause were reported for 44% of the **BOTOX®**-treated subjects and 42% of the placebo-treated subjects. The incidence of blepharoptosis was higher in the **BOTOX®**-treated arm than in placebo (3.2% vs 0%, p value = 0.045).

In the open-label, repeat injection study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not be predictive of rates observed in practice.

Randomized Double-Blind Studies: Rates of Adverse Events Reported by >2 or more Subjects in the **BOTOX®** Group, by Treatment Group.

| Adverse Event (in order of decreasing frequency for **BOTOX®**) | **BOTOX®** (N=405) | Placebo (N=130) |
|---|---|---|
| Overall | 177 (43.7%) | 54 (41.5%) |
| Body as a Whole: | | |
| Headache | 54 (13.3%) | 23 (17.7%) |
| Pain in Face | 9 (2.2%) | 1 (0.8%) |
| Flu Syndrome | 8 (2.0%) | 2 (1.5%) |
| Pain at Injection Site | 7 (1.7%) | 1 (0.8%) |
| Edema at Injection Site | 6 (1.5%) | 3 (2.3%) |
| Pain in Back | 4 (1.0%) | 3 (2.3%) |
| Injury accidental | 3 (0.7%) | 1 (0.8%) |
| Respiratory System: | | |
| Infection | 14 (3.5%) | 5 (3.8%) |
| Bronchitis | 6 (1.5%) | 1 (0.8%) |
| Sinusitis | 6 (1.5%) | 1 (0.8%) |
| Pharyngitis | 5 (1.2%) | 2 (1.5%) |
| Dyspnea | 3 (0.7%) | 0 (0.0%) |
| Infection sinus | 3 (0.7%) | 2 (1.5%) |
| Laryngitis | 3 (0.7%) | 0 (0.0%) |

| | | |
|---|---|---|
| Rhinitis | 3 (0.7%) | 2 (1.5%) |
| Skin and Appendages: | | |
| Erythema | 7 (1.7%) | 2 (1.5%) |
| Skin Tightness | 4 (1.0%) | 0 (0.0%) |
| Irritation Skin | 3 (0.7%) | 0 (0.0%) |
| Digestive System: | | |
| Nausea | 12 (3.0%) | 3 (2.3%) |
| Dyspepsia | 4 (1.0%) | 0 (0.0%) |
| Tooth Disorder | 4 (1.0%) | 0 (0.0%) |
| Liver Function Abnormal | 3 (0.7%) | 2 (1.5%) |
| Special Senses: | | |
| Blepharoptosis | 13 (3.2%) | 0 (0.0%) |
| Nervous System: | | |
| Dizziness | 5 (1.2%) | 2 (1.5%) |
| Paresthesia | 4 (1.0%) | 1 (0.8%) |
| Anxiety | 3 (0.7%) | 0 (0.0%) |
| Twitch | 3 (0.7%) | 0 (0.0%) |
| Musculoskeletal System: | | |
| Muscle Weakness | 8 (2.0%) | 0 (0.0%) |
| Urogenital System: | | |
| Infection Urinary Tract | 4 (1.0%) | 1 (0.8%) |
| Hemic and Lymphatic System: | | |
| Ecchymosis | 7 (1.7%) | 3 (2.3%) |
| Cardiovascular: | | |
| Hypertension | 4 (1.0%) | 0 (0.0%) |

In published literature of the use of botulinum toxin type A for facial lines, there has been a single reported incident of diplopia, which resolved completely in three weeks. Transient ptosis, the most frequently reported complication, has been reported in the literature in approximately 5% of patients.

***Lateral Canthal Lines***

The table below lists selected adverse reactions reported within 90 days following injection by ≥ 1% of **BOTOX®** treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of **BOTOX®** in the improvement of the appearance of lateral canthal lines alone.

Adverse Reaction Reported by ≥1% of **BOTOX®** treated Patients and More Frequent than in Placebo-treated Patients Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Lateral Canthal Lines:

| Adverse Reactions by System Organ Class | **BOTOX®** 24 Units (N=526) | Placebo (N=530) |
|---|---|---|
| Eye Disorders | | |
| Eyelid edema | 5 (1%) | 0 (0%) |

***Forehead Lines***

The table below presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical studies following injection of BOTOX® for forehead lines with glabellar lines.

Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies

| Adverse Reactions by System Organ Class | BOTOX® (20 Units forehead lines with 20 Units glabellar lines) (N=665) | Placebo (N=315) |
|---|---|---|
| Nervous System Disorders<br>Headache | 58 (8.7%) | 17 (5.4%) |
| Eye Disorders<br>Eyelid ptosis | 12 (1.8%) | 1 (0.3%) |
| Skin and Subcutaneous Tissue Disorders<br>Brow ptosis<br>Skin tightness (including Mephisto Sign) | 13 (2.0%)<br>10 (1.5%) | 0 (0%)<br>0 (0%) |

There were no additional adverse drug reactions reported with the simultaneous treatment of Facial Lines (inclusive of forehead lines, glabellar lines, and lateral canthal lines).

**Immunogenicity**

Treatment with **BOTOX®** for cosmetic purposes may result in formation of neutralizing antibodies to botulinum toxin type A that may reduce the effectiveness of **BOTOX®** treatment and subsequent treatments of **BOTOX®** for the appearance of glabellar lines and the effectiveness of **BOTOX®** in the treatment of other clinical indications such as cervical dystonia, blepharospasm and strabismus by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX®** has not been well studied.

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with **BOTOX®** had specimens analyzed for antibody formation. Among the 916 **BOTOX®** treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

The presence of antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX®** Purified Neurotoxin Complex therapy. In clinical studies, reduction in effectiveness due to antibody production has occurred in one patient with blepharospasm receiving 3 doses of **BOTOX®** over a 6-week period totaling 92 U, and several patients with torticollis who received multiple doses experimentally, totaling over 300 U in a one-month period. For this reason, the dose of BOTOX® for blepharospasm should be kept as low as possible, in any case below 200 U in a one-month period.

The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to **BOTOX®** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody

(including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to **BOTOX®** with the incidence of antibodies to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies of the use of **BOTOX®** in the treatment of other clinical indications suggest that **BOTOX®** injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential of antibody formation may be minimized by injecting the lowest effective dose given at the longest feasible intervals between injections.

**Postmarketing Experience**

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia and/or other significant debility, after treatment with Botox.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX® inappropriately diluted with 5 ml of 1% lidocaine. The causal role of BOTOX®, lidocaine, or both cannot be reliably determined

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes following BOTOX® treatment. Some of these patients had risk factors including cardiovascular disease.

New onset or recurrent seizures have also been reported following BOTOX® treatment, typically in patients who are predisposed to experiencing these events.

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

Lagophthalmos has been reported following Botox® injection into glabellar lines.

Eyelid edema has been reported following periocular BOTOX® injection.

Mephisto sign has been reported for glabellar lines indications following BOTOX® injection into or near the frontalis muscle.

The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in Section Warnings and Precautions, and Section Adverse Reactions: allergic reaction; denervation/muscle atrophy; respiratory depression and/or respiratory failure; dyspnea; aspiration pneumonia; dysarthria; dysphonia; dry mouth; strabismus; peripheral

neuropathy, abdominal pain; diarrhea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance; hypoacusis; tinnitus; vertigo; vertigo with nystagmus, facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoesthesia; malaise; myalgia; myasthenia gravis; paresthesia; rash; erythema multiforme; pruritus; dermatitis psoriasiform; psoriasiform eruption; hyperhidrosis; alopecia; including madarosis; decreased hearing, ear noise; localized numbness, retinal vein occlusion, dry eyes and localized muscle twitching/involuntary muscle contractions.

**Reporting of Suspected Adverse Reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the following:

National reporting system: https://e-meso.pom.go.id/subsite/ and/or to pv-center@pom.go.id

Pharmaceutical industry reporting system:
Telephone: +62 21 21684084
or
Email: IDsafety@zuelligpharma.com

**Pharmacodynamic Properties**

**BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, **BOTOX®** produces a localized chemical denervation muscle paralysis. When the muscle is chemically denervated, it atrophies and may develop extrajunctional acetylcholine receptors. There is evidence that the nerve can sprout and reinnervate the muscle, with the weakness thus being reversible.

In sensory neurons, BOTOX® inhibits the release of sensory neurotransmitters (e.g., Substance P, CGRP) and downregulates the expression of cell surface receptors (e.g., TRPV1). BOTOX® also prevents and reverses sensitization in nociceptive sensory neurons.

The paralytic effect on muscle injected with **BOTOX®** Purified Neurotoxin Complex is useful in reducing the excessive, abnormal contractions associated with blepharospasm. When used for the treatment of strabismus, it is postulated that the administration of **BOTOX®** affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the muscle's antagonist. Following peri-ocular injection of **BOTOX®**, distant muscles show electrophysiologic changes but no clinical weakness or other clinical change for a period of several weeks or months, parallel to the duration of local clinical paralysis.

**Forehead Lines**

Two multicenter, randomized, double-blind, placebo-controlled studies evaluated BOTOX® (N=921, randomized to receive any BOTOX® treatment or N=257, randomized to receive placebo) for the temporary improvement in the appearance of moderate to severe forehead lines (FHL).

Study 1 assessed BOTOX® treatment of FHL with glabellar lines (GL); Study 2 also assessed simultaneous treatment of upper facial lines (FHL, GL, and crow's feet lines [CFL]). The primary efficacy measure was the assessment of FHL severity at maximum eyebrow elevation using the 4-point Facial Wrinkle Scale with Photonumeric Guide (FWS; 0=none, 1=mild, 2=moderate, 3=severe). The primary efficacy response definition used for the pivotal trials was a composite ≥ 2-grade improvement from baseline in FHL severity at maximum eyebrow elevation, assessed independently by both investigator and patient. The primary timepoint was Day 30 following the first treatment.

**Studies 1 and 2: Composite Investigator and Patient Assessment of FHL Severity at Maximum Eyebrow Elevation at Day 30 – Responder Rates (% and Number of Patients Achieving ≥ 2-Grade Improvement from Baseline)**

| | Study 1 | | | Study 2 | | | | |
|---|---|---|---|---|---|---|---|---|
| **Day** | **TN 40 Units (20 Units FHL with 20 Units GL) (N=290)** | **Placebo (N=101)** | **P-value 40 Units vs placebo** | **TN 40 Units (20 Units FHL with 20 Units GL) (N=318)** | **TN 64 Units (20 Units FHL, 20 Units GL, and 24 Units CFL) (N=313)** | **Placebo (N=156)** | **P-value 40 Units vs placebo** | **P-value 64 Units vs placebo** |
| 7 | 52.8% (153/290) | 0.0% (0/101) | <0.0001 | 38.4% (122/318) | 40.6% (127/313) | 0.0% (0/156) | <0.0001 | <0.0001 |
| 14 | 64.1% (186/290) | 0.0% (0/101) | <0.0001 | 47.5% (151/318) | 53.4% (167/313) | 0.0% (0/156) | <0.0001 | <0.0001 |
| 30 | 61.4% (178/290) | 0.0% (0/101) | <0.0001 | 45.6% (145/318) | 53.0% (166/313) | 0.6% (1/156) | <0.0001 | <0.0001 |
| 60 | 37.2% (108/290) | 0.0% (0/101) | <0.0001 | 26.7% (85/318) | 33.9% (106/313) | 0.0% (0/156) | <0.0001 | <0.0001 |
| 90 | 13.4% (39/290) | 0.0% (0/101) | 0.0001 | 12.6% (40/318) | 14.1% (44/313) | 0.0% (0/156) | <0.0001 | <0.0001 |
| 120 | 5.2% (15/290) | 0.0% (0/101) | 0.0259 | 3.5% (11/318) | 8.3% (26/313) | 0.0% (0/156) | 0.0222 | 0.0002 |
| 150 | 1.0% (3/290) | 0.0% (0/101) | 0.3053 | 0.6% (2/318) | 1.6% (5/313) | 0.0% (0/156) | 0.3094 | 0.1705 |
| 180 | 0.0% (0/290) | 0.0% (0/101) | NA | 0.3% (1/318) | 0.3% (1/313) | 0.0% (0/156) | 0.4795 | 0.4795 |

Source: Module 2.7.3 Summary of Clinical Efficacy Tables 2-7 and 2-10

Studies 1 and 2 showed a decrease in number of responders for the primary endpoint from Day 30.

The duration of effect based on statistical significance versus placebo was 4 months for the primary composite efficacy variable for Studies 1 and 2.

A total of 165 and 197 patients received 3 cycles over 1 year of BOTOX®. The response rate for FHL was similar across all treatment cycles.

**Blepharospasm**
In one study, botulinum toxin was evaluated in 27 patients with essential blepharospasm. Twenty-six of the patients had previously undergone drug treatment utilizing benztropine mesylate, clonazepam and/or baclofen without adequate clinical results. Three of these patients then underwent muscle stripping surgery still without an adequate outcome. One patient of the 27 was previously untreated. Upon using botulinum toxin, 25 of the 27 patients reported improvement within 48 hours. One of the other patients was later controlled with a higher dosage. The remaining patient reported only mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. All patients receiving botulinum toxin (n=8) were improved compared with no improvements in the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.

One thousand six hundred eighty-four patients with blepharospasm evaluated in an open trial showed clinical improvement lasting an average of 12.5 weeks prior to the need for re-treatment.

**Strabismus**
Six hundred seventy-seven patients with strabismus treated with one or more injections of **BOTOX®** Purified Neurotoxin Complex were evaluated in an open trial. Fifty-five percent of these patients were improved to an alignment of 10 prism diopters or less when evaluated 6 months or more following injection. These results are consistent with results from additional open-label trials which were conducted for this indication.

**Pharmacokinetic Properties**

Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels following IM injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness. These side effects may be due to local spread of toxin from the injection site and/or misplaced injections.

Clinical studies have reported changes in clinical electromyographic parameters (i.e., jitter) in muscles distant to the site of **BOTOX®** injection. This may indicate spread of the toxin via

circulation, retro- or ortho-grade axonal transport, or some action of the toxin at a third, central, or unidentified site.

**Overdose**

Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis which could be local, or distant from the site of injection which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness or respiratory failure.

An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. In the event of an overdose or injection into the wrong muscle, immediately contact Allergan for additional information at 1-800-678-1605 from 7:00 AM to 3:00 PM Pacific Time. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

**Instructions for Use, Handling and Disposal**

Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter.

The primary release procedure for Botox® uses a cell-based potency assay to determine the potency relative to a reference standard. This assay is specific to Allergan's product Botox®**.** Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various potency assays, Units of biological activity of Botulinum Toxin Type A cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal dose-activity relationship to human dose relationships.

***Dilution Technique***

To reconstitute lyophilized **BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex, use sterile normal saline without a preservative: 0.9% Sodium Chloride injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since **BOTOX®** is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and

time of reconstitution on the space on the label. **BOTOX®** should be administered within 4 hours after reconstitution.

During this time period, reconstituted **BOTOX®** Purified Neurotoxin Complex should be stored in a refrigerator (2˚C to 8˚C). Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit. The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative.

***Dilution Table***

**Dilution Table for 50 Unit, 100 Unit, and 200 Unit Vials**

| Diluent Added (0.9% Sodium Chloride Injection) | 50 Unit Vial | 100 Unit Vial | 200 Unit Vial |
|---|---|---|---|
| | Resulting dose/ Units per 0.1 mL | Resulting dose/ Units per 0.1 mL | Resulting dose/ Units per 0.1 mL |
| 0.5 mL | 10 | - | - |
| 1.0 mL | 5 | 10 | - |
| 2.0 mL | 2.5 | 5 | 10 |
| 4.0 mL | 1.25 | 2.5 | 5 |
| 8.0 mL | NA | 1.25 | 2.5 |
| 10.0 mL | NA | 1 | 2 |

***Note:*** These dilutions are calculated for an injection volume of 0.1 mL. A decrease in the **BOTOX®** Purified Neurotoxin Complex dose is also possible by administering a smaller or larger injection volume from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

Using a 21-gauge, 2.5”-length needle and an appropriately sized syringe draw up a total of 2.5 mL of 0.9% sterile saline. Insert the needle at a 45˚ angle and slowly inject into the **BOTOX®** vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently rotate the vial and record the date and time of reconstitution on the space on the label.

Draw at least 0.5 mL of the properly reconstituted toxin into the sterile syringe, preferably a tuberculin syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-gauge needle.

Confirm the patency of the needle.

**How Supplied**

**BOTOX®** is supplied as a single patient use vial. The product and diluent do not contain a preservative. Once opened and reconstituted it should be stored in a refrigerator (2˚C to 8˚C) and used within four hours. Discard any remaining solution. Parenteral drug products should be

inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not freeze reconstituted **BOTOX®**.

Each vial of BOTOX® 50 Units contains 50 Units of vacuum-dried ***Clostridium botulinum*** Toxin Type A.

Each vial of BOTOX® 100 Units contains 100 Units of vacuum-dried ***Clostridium botulinum*** Toxin Type A.

Each vial of BOTOX® 200 Units contains 200 Units of vacuum-dried ***Clostridium botulinum*** Toxin Type A.

**Storage Conditions**

Store unopened vial in refrigerator (2˚ to 8˚C). Administer **BOTOX®** (Botulinum Toxin Type A) Purified Neurotoxin Complex within 4 hours after the vial is removed from the refrigerator and reconstituted. During these four hours, reconstituted **BOTOX®** should be stored in a refrigerator (2˚ to 8˚C). Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as medical waste. In cases when deactivation of the toxin is desired (e.g. spills), the use of dilute hypochlorite solution (0.5% or 1%) for five minutes is recommended prior to disposal as medical waste.

***Shelf life***
36 months

**Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.**

Manufactured by : Allergan Pharmaceuticals Ireland

Westport, Co. Mayo, Ireland

Imported by : PT. Tunggal Idaman Abdi

Jl. Jend. Ahmad Yani No.7

Jakarta 13230

INDONESIA

(Harus dengan resep dokter)

Reg No. Botox 50: DKI2281501044B1

Reg No. Botox 100: DKI2281501044A1

Reg No. Botox 200: DKI2381501044C1

Date of Revision: 16 June 2025

abbvie

# BOTOX®

**(Botulinum Toxin Type A)**
**Purified Neurotoxin Complex**

**Leaflet Kemasan: Informasi untuk pengguna**

BOTOX®, 50 Unit, Serbuk Injeksi
BOTOX®, 100 Unit, Serbuk Injeksi
BOTOX®, 200 Unit, Serbuk Injeksi
Toksin Botulinum tipe A

**Baca seluruh isi leaflet ini dengan seksama sebelum anda mulai menggunakan obat ini karena leaflet ini mengandung informasi penting untuk anda.**

- Simpan leaflet ini. Anda mungkin memerlukannya lagi di suatu saat.
- Apabila anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker anda.
- Obat ini diresepkan hanya untuk anda. Jangan berikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka, meskipun mereka memiliki gejala penyakit yang sama seperti anda.
- Apabila anda mengalami efek samping, bicarakan pada dokter, apoteker, atau perawat anda. Hal ini termasuk efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

**Yang terkandung dalam leaflet ini:**



## 1. Apa itu BOTOX® dan apa kegunaannya

BOTOX® adalah relaksan otot yang digunakan untuk mengatasi beberapa kondisi tubuh. BOTOX® mengandung substansi aktif berupa toksin Botulinum tipe A dan disuntikkan pada otot atau ke bagian dalam kulit. BOTOX® bekerja dengan cara menyekat secara parsial impuls saraf pada otot yang telah disuntik dan mengurangi kontraksi berlebih pada otot-otot tersebut.

BOTOX® dapat disuntikkan langsung pada otot dan dapat digunakan untuk:

- Mengobati masalah kelainan tertentu pada otot mata atau mata juling (strabismus) atau kekakuan pada kelopak mata yang tidak normal (blefarospasme) pada usia 12 tahun dan lebih.
- Memperbaiki penampakan garis kerut diantara kedua alis (garis glabelar), pada derajat sedang sampai berat pada dewasa di bawah usia 65 tahun, untuk jangka waktu singkat (sementara).
- Memperbaiki penampakan garis-garis seperti kipas pada sudut mata (garis cakar ayam) pada dewasa untuk jangka waktu singkat (sementara).
- Memperbaiki penampakan garis-garis dahi pada dewasa untuk jangka waktu singkat (sementara)

## 2. Apa yang perlu anda ketahui sebelum menggunakan BOTOX®

### Jangan gunakan BOTOX®

- Apabila anda alergi (hipersensitif) terhadap toksin botulinum tipe A atau bahan-bahan lain yang terkandung pada obat ini (tertera pada bagian 6) dan jika adanya infeksi pada bagian yang akan disuntikkan;

### Peringatan dan pencegahan

**Bicarakan dengan dokter atau apoteker anda sebelum menggunakan BOTOX®:**

- Apabila anda pernah mengalami masalah bernafas, menelan, atau berbicara. Masalah-masalah ini dapat terjadi dalam hitungan jam, hari, atau minggu setelah suntikkan BOTOX®, biasanya terjadi karena otot yang anda gunakan untuk bernafas atau menelan dapat menjadi lemah setelah suntikkan. Kematian dapat terjadi karena komplikasi apabila anda memiliki masalah serius pada fungsi menelan atau bernafas setelah pengobatan dengan BOTOX®;
- Apabila anda **berusia lebih dari 65 tahun** dan memiliki penyakit serius;
- Apabila anda menderita **penyakit otot lain** atau penyakit kronis yang menyerang otot (seperti miastenia gravis atau Sindrom Lambert-Eaton);
- Menderita **penyakit** tertentu yang menyerang **sistem saraf** (seperti *amyotropic lateral scleroris* atau neuropati motoris);
- Apabila anda memiliki **kelemahan** atau **penyusutan otot** yang signifikan di tempat yang akan disuntik dokter;
- Apabil anda pernah menjalani **operasi** yang mengubah otot yang akan disuntik;
- Apabila anda sebelumnya pernah memiliki **masalah dengan penyuntikkan** (seperti pingsan);
- Apabila anda memiliki **peradangan pada otot atau kulit** di tempat yang akan disuntik dokter;
- Apabila anda pernah memiliki masalah dengan penyuntikkan toksin botulinum sebelumnya;
- Apabila anda menderita penyakit kardiovaskuler (penyakit jantung dan pembuluh darah);

***Setelah anda mendapatkan suntikan BOTOX®***

**Anda atau perawat anda sebaiknya menghubungi dokter dan mencari pertolongan medis segera apabila anda mengalami hal-hal berikut:**

- Kesulitan **bernafas, menelan, atau berbicara**;
- **Gatal-gatal, bengkak** termasuk bengkak pada wajah atau tenggorokan, **mengi, rasa lemah** dan **nafas pendek** (kemungkinan gejala reaksi alergi berat)

***Pencegahan umum***

Sama seperti suntikan lainnya, prosedur ini dapat menyebabkan infeksi, nyeri, bengkak, rasa terbakar dan tersengat, peningkatan sensitifitas, lembek, kemerahan, dan/atau perdarahan/memar pada lokasi penyuntikkan.

Efek samping yang mungkin terkait dengan penyebaran toksin pada tempat yang jauh dari lokasi penyuntikkan pernah dilaporkan (sebagai contoh kelemahan otot, kesulitan menelan atau ditemukannya makanan atau cairan yang tidak diinginkan pada jalan nafas). Hal ini kadang-kadang merupakan risiko pada pasien dengan penyakit dasar yang membuat mereka lebih rentan terkena gejala-gejala diatas.

Apabila anda diberikan BOTOX® terlalu sering atau dengan dosis yang terlalu tinggi, kemungkinan anda dapat mengalami kelemahan otot atau efek samping terkait dengan penyebaran toksin, atau tubuh anda mungkin mulai memproduksi antibodi yang dapat menurunkan efek dari BOTOX®. Untuk menurunkan risiko ini, interval dari dua pengobatan tidak boleh kurang dari tiga bulan, sesuai indikasi pengobatan.

Apabila BOTOX® digunakan dalam pengobatan penyakit yang tidak tertera pada leaflet ini, BOTOX® dapat menyebabkan reaksi serius, terutama pada pasien yang tengah mengalami kesulitan bernafas atau kelemahan tubuh yang signifikan.

Apabila anda belum melakukan olahraga dalam waktu yang lama sebelum menerima pengobatan BOTOX®, anda sebaiknya mulai berolahraga secara bertahap setelah mendapat suntikan.

Saat BOTOX®digunakan pada pengobatan spasme otot kelopak mata yang persisten, hal ini dapat menyebabkan berkurangnya frekuensi kedipan mata. yang dapat berbahaya bagi permukaan bola mata anda. Untuk mencegah hal ini, anda mungkin memerlukan pengobatan dengan tetes mata atau salep mata, lensa kontak lembut, atau penutup mata agar mata anda dalam keadaan tertutup. Dokter anda akan memberitahukan anda apabila hal-hal ini diperlukan.

Saat BOTOX® digunakan pada pengobatan garis-garis vertikal dan garis berbentuk kipas pada sudut mata, penurunan kelopak mata dapat terjadi setelah pengobatan. Gejala Mephisto (Terangkatnya alis bagian luar) telah dilaporkan untuk pengobatan garis-garis vetikal setelah penyuntikan BOTOX® ke dalam atau di dekat otot frontalis

**Obat-obatan lain dengan BOTOX®**

**Beritahukan dokter** atau apoteker apabila:

- Anda menggunakan **antibiotik** (digunakan untuk mengobati infeksi), atau obat-obatan lain yang mempengaruhi saraf yang mengontrol otot (contohnya obat-obatan **anticholinesterase** atau **relaksan otot**). Beberapa obat-obatan ini dapat meningkatkan efek BOTOX®.
- Anda baru-baru ini disuntik dengan obat yang mengandung toksin botulinum (substansi aktif BOTOX®), karena hal ini dapat meningkatkan efek BOTOX® secara berlebihan.
- Anda menggunakan produk anti-platelet (mirip aspirin) dan/atau antikoagulan (pengencer darah)

Beritahukan dokter atau apoteker anda apabila anda sedang atau baru-baru ini atau kemungkinan menggunakan obat-obatan lain.

**Kehamilan dan menyusui**

Penggunaan BOTOX® tidak direkomendasikan selama kehamilan. Tidak diketahui apakah BOTOX® dikeluarkan melalui air susu ibu.

Apabila anda sedang hamil atau menyusui, atau merasa anda mungkin hamil atau berencana untuk hamil, tanyakan pada dokter atau apoteker anda sebelum menggunakan obat ini.

**Mengemudi dan menggunakan alat berat**

BOTOX® dapat menyebabkan pusing, rasa kantuk, lelah, dan masalah penglihatan. Apabila anda mengalami efek samping ini, jangan mengemudi atau mengoperasikan alat-alat berat. Apabila anda tidak yakin, konsultasikan dengan dokter anda.

## 3. Bagaimana menggunakan BOTOX®

BOTOX® hanya dapat disuntikkan oleh dokter dengan keterampilan khusus dan pengalaman dalam menggunakan obat ini.

**Metode dan rute administrasi**

BOTOX® disuntikkan pada otot anda (intramuskuler). BOTOX® disuntikkan langsung pada area yang dimaksud; dokter anda biasanya akan menyuntikkan **BOTOX® pada beberapa titik dalam area yang dimaksud**.

**Informasi umum tentang dosis**

- Jumlah suntikan untuk setiap otot dan dosis berbeda-beda tergantung indikasi. Untuk itu, dokter anda akan menentukan berapa banyak, seberapa sering, dan pada otot mana BOTOX® akan diberikan. Direkomendasikan agar dokter anda menggunakan dosis efektif terendah;

- Dosis untuk orang usia lanjut sama dengan dosis orang dewasa.

Dosis BOTOX® dan durasi dari efeknya akan berbeda-beda tergantung pada kondisi pengobatan. Di bawah ini adalah detail dari kondisi-kondisi tersebut.

Keamanan dan efektivitas BOTOX® belum dapat ditentukan untuk anak-anak/remaja di bawah usia berikut:

| | |
|---|---|
| Masalah otot penggerak bola mata tertentu (strabismus) atau spasme kelopak mata tidak normal (blefarospasme) | 12 tahun |
| Garis kerut diantara alis (garis glabelar), garis-garis berbentuk kipas pada sudut mata (garis cakar ayam) dan garis-garis dahi | 18 tahun |

Sebagai tambahan, terdapat sangat sedikit pengalaman dalam penggunaan BOTOX® untuk mengobati garis kerut pada pasien berusia lebih dari 65 tahun.

Untuk masalah otot mata tertentu (strabismus), anda akan merasakan efek mulai dari 1 sampai 2 hari setelah suntikkan dengan intensitas yang meningkat selama minggu pertama dan bertahan sampai 2 hingga 6 minggu lalu turun bertahap dalam waktu yang bersamaan. Koreksi berlebih yang bertahan lebih dari 6 bulan tergolong jarang. Kurang lebih setengah pasien memerlukan dosis berikutnya karena respons yang inadekuat terhadap dosis inisial, atau karena faktor mekanis.

Untuk spasme kelopak mata tidak normal (blefarospasme), perbaikan akan terlihat dalam waktu 3 hari setelah penyuntikkan dan efek maksimum dapat dilihat setelah 1 sampai 2 minggu. Pembentukan antibodi mungkin mengurangi efektivitas pengobatan dan ini harus dipertimbangkan ketika merencanakan dosis pengobatan di masa depan. Oleh itu, dosis kumulatif untuk pengobatan blefarospasme tidak boleh melebihi 200 Unit dalam periode 30 hari.

Untuk **garis vertikal diantara alis**, anda dapat melihat perbaikan dalam 1 minggu setelah pengobatan. Efek pengobatan dapat terlihat sampai 4 bulan setelah penyuntikkan.

Untuk **garis dahi**, waktu penyuntikan ulang BOTOX® adalah sekitar 4 bulan. Keamanan dan efektifitas penggunaan BOTOX® lebih sering dari pada setiap 3 bulan belum dievaluasi secara klinis.

**Apabila anda menerima BOTOX® lebih dari jumlah yang seharusnya**

Tanda-tanda penggunaan BOTOX® yang berlebih kemungkinan tidak muncul sampai beberapa hari setelah penyuntikkan. Apabila anda menelan BOTOX® atau tidak

sengaja menyuntikkan BOTOX®, anda harus segera menemui dokter anda yang dapat memantau kondisi anda selama beberapa minggu.

Apabila anda menerima terlalu banyak BOTOX®, anda dapat mengalami gejala-gejala di bawah ini dan anda harus menghubungi dokter anda segera. Dokter anda akan menentukan apakah anda perlu pergi ke rumah sakit:

- Kelemahan otot yang bersifat lokal atau jauh dari lokasi penyuntikkan;
- Kesulitan bernafas, menelan, atau berbicara karena kelumpuhan otot;
- Makanan atau cairan yang secara tidak sengaja masuk ke paru-paru yang dapat menyebabkan pneumonia (infeksi paru) akibat kelumpuhan otot;

Apabila anda memiliki pertanyaan lebih lanjut mengenai penggunaan produk ini, tanyakan pada dokter atau apoteker anda.

## 4. Efek samping yang mungkin terjadi

**Apabila anda memiliki kesulitan bernafas, menelan, atau berbicara setelah menerima suntikkan BOTOX®, hubungi dokter anda segera**.

**Apabila anda mengalami gatal-gatal, bengkak termasuk bengkak pada wajah atau tenggorokkan, mengi, pandangan ganda, lemas, dan kesulitan bernafas, hubungi dokter anda segera.**

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya. Secara umum, efek samping terjadi dalam beberapa hari pertama setelah penyuntikkan.

Efek samping ini biasanya bertahan dalam jangka waktu pendek, namun efek samping dapat bertahan hingga beberapa bulan dan bahkan lebih lama lagi pada kasus-kasus tertentu.

Seperti yang diperkirakan pada prosedur penyuntikkan lainnya, rasa nyeri/terbakar/tersengat, bengkak, kelemahan otot, kelelahan, dan atau memar dapat diasosiasikan dengan penyuntikkan.

Efek samping dapat diklasifikasikan menjadi kategori-kategori berikut, tergantung dari seberapa sering efek samping in terjadi:

| | |
|---|---|
| Sangat sering | Mempengaruhi lebih dari 1 dari 10 orang |
| Sering | Mempengaruhi hingga 1 dari 10 orang |
| Tidak sering | Mempengaruhi hingga 1 dari 100 orang |
| Jarang | Mempengaruhi hingga 1 dari 1000 orang |
| Sangat jarang | Mempengaruhi hingga 1 dari 100000 orang |

Dibawah ini adalah daftar efek samping yang bervariasi tergantung pada bagian tubuh dimana BOTOX® disuntikkan. Apabila efek samping ini menjadi serius, atau apabila anda merasakan efek samping yang tidak tertera dalam leaflet ini, beritahukan pada dokter atau apoteker anda.

**Injeksi (suntikan) untuk masalah pada otot bola mata**

| | |
|---|---|
| Sangat sering | • Kelopak mata terkulai<br>• Bola mata bergerak ke atas |

**Injeksi (suntikan) pada spasme otot kelopak mata**

| | |
|---|---|
| Sangat sering | • Kelopak mata terkulai |
| Sering | • Bengkak pada wajah<br>• Kesulitan untuk menutup mata sepenuhnya<br>• Air mata yang berlebih<br>• Mata kering<br>• Iritasi mata<br>• Sensitivitas terhadap cahaya |

**Injeksi (suntikkan) pada dahi untuk garis-garis vertikal**

| | |
|---|---|
| Sangat sering | • Sakit kepala |
| Sering | • Nyeri pada lokasi suntikan<br>• Terkulainya kelopak mata<br>• Bengkak pada lokasi suntikan<br>• Kelemahan otot terlokalisasi<br>• Nyeri wajah<br>• Nyeri punggung<br>• Mual<br>• Dispepsia (masalah pencernaan)<br>• Kelainan gigi<br>• Infeksi saluran kemih<br>• Memar di bawah kulit (ekimosis)<br>• Kemerahan pada kulit<br>• Infeksi pernafasan |

**Injeksi (suntikan) pada garis-garis berbentuk kipas dari sudut mata**

| | |
|---|---|
| Sering | • Bengkak pada kelopak mata |

**Injeksi (suntikan) pada garis-garis dahi.**

| | |
|---|---|
| Sering | • Sakit Kepala<br>• Terkulainya kelopak mata<br>• Terkulainya alis<br>• Kulit yang kencang/ tegang (termasuk gejala mephisto) |

Daftar berikut ini memuat efek samping obat atau kejadian tidak diinginkan lainnya yang relevan secara medis yang telah dilaporkan sejak obat dipasarkan, tanpa memandang indikasinya, dan bisa jadi menambahkan apa yang telah dikutip di Bagian Efek Samping: reaksi alergi; penurunan masa otot; depresi pernapasan dan/atau gagal

napas; sesak napas; peradangan paru karena adanya benda asing; gangguan proses bicara; gangguan pita suara; mulut kering; mata juling; gangguan sistem saraf perifer, nyeri abdomen; diare; mual; muntah; demam; anoreksia; penglihatan kabur; gangguan penglihatan; gangguan pendengaran; telinga berdenging; vertigo; vertigo disertai pergerakan bola mata yang tidak normal, lumpuh wajah, melemahnya otot wajah; gangguan saraf perifer yang mengenai pleksus brakialis; saraf terjepit; pingsan; berkurangnya sensasi raba; perasaan tidak nyaman/lesu; nyeri otot atau pegal-pegal; miastenia gravis; kesemutan; ruam; ruam karena infeksi atau pengobatan; gatal-gatal; dermatitis psoriasiformis; erupsi psoriasiformis; keringat berlebih; kerontokan rambut; termasuk kerontokan bulu mata; penurunan pendengaran; suara bising di telinga; kekebasan lokal; sumbatan vena retina, mata kering, dan kedutan otot lokal/kontraksi otot tidak disengaja.

**Pelaporan efek samping**
Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini.
Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut:
Telepon: +62 21 21684084 atau
Email: IDsafety@zuelligpharma.com.

Dengan melaporkan efek samping Anda dapat membantu menyediakan informasi keamanan lebih lanjut dari obat ini.

## 5. Bagaimana cara penyimpanan BOTOX®

Jauhkan dari pandangan dan jangkauan anak-anak.
Simpan vial yang belum dibuka pada lemari pendingin (2°C – 8°C).
Setelah larutan dibuat, gunakan larutan segera; namun demikian larutan dapat disimpan sampai 4 jam dalam lemari pendingin (2°C – 8°C).

Dokter anda tidak disarankan menggunakan BOTOX® setelah lewat tanggal kadaluarsa yang tertera pada label ‘EXP’. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

## 6. Isi kemasan dan informasi lainnya

**Apa yang dikandung BOTOX®**

- Substansi aktif: Toksin Botulinum tipe A dari *Clostridium botulinum*.
- Komposisi lainnya adalah albumin manusia dan natrium klorida.

**Seperti apa bentuk BOTOX® serta isi kemasan obat**

BOTOX® disajikan sebagai bubuk berwarna putih dalam vial kaca transparan.
Sebelum penyuntikkan, produk ini harus dilarutkan dalam larutan salin steril.
Setiap vial mengandung baik 50, 100 atau 200 Unit toksin Botulinum tipe A.
Setiap kemasan mengandung 1, 2, 3, atau 6 vial. Tidak semua ukuran kemasan dipasarkan.

**Pemegang Izin Edar dan Pembuatan**

Pemegang Otorisasi Pemasaran:
PT. Tunggal Idaman Abdi
Jl. Jend. Ahmad Yani No.7
Jakarta 13230
INDONESIA

Pembuatan:
Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
County Mayo
Irlandia

Nomor Otorisasi Pemasaran:
BOTOX® 50 DKI2281501044B1
BOTOX® 100 DKI2281501044A1
BOTOX® 200 DKI2381501044C1
Peringatan khusus
HARUS DENGAN RESEP DOKTER

Leaflet ini terakhir direvisi pada 3 Juli 2025

**Pada proses pembuatannya bersinggungan dengan bahan bersumber babi**