



BOTOX® Cosmetic Indications

BOTOX® Cosmetic (onabotulinumtoxinA) is indicated in adult patients for the temporary improvement in the appearance of:

- moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity
- moderate to severe lateral canthal lines associated with orbicularis oculi activity
- moderate to severe forehead lines associated with frontalis activity

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

Warning: Distant Spread of Toxin Effect

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

CONTRAINDICATIONS

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

Intradetrusor injection of BOTOX® is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection (UTI). Intradetrusor injection of BOTOX® is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200 mL, who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

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

Spread of Toxin Effect

Please refer to Boxed Warning for Distant Spread of Toxin Effect.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX® Cosmetic at the labeled dose of 20 Units (for glabellar lines), 24 Units (for lateral canthal lines), 40 Units (for forehead lines with glabellar lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines), and 64 Units (for simultaneous treatment of lateral canthal lines, glabellar lines, and forehead lines), or at the labeled dose of 100 Units (for severe primary axillary hyperhidrosis) have been reported.

Serious Adverse Reactions With Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX® injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX® to the site of injection and/or adjacent structures. In several of the cases, patients had

pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX®. The safety and effectiveness of BOTOX® for unapproved uses have not been established.

Hypersensitivity Reactions

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

Cardiovascular System

There have been reports following administration of BOTOX® 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. Use caution when administering to patients with pre-existing cardiovascular disease.

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

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from onabotulinumtoxinA (see Warnings and Precautions).

Dysphagia and Breathing Difficulties

Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see Boxed Warning).

Pre-existing Conditions at the Injection Site

Caution should be used when BOTOX® Cosmetic treatment 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(s).

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral disease and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

ADVERSE REACTIONS

The following adverse reactions to BOTOX® and BOTOX® Cosmetic for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning); Hypersensitivity Reactions (see *Contraindications and Warnings and Precautions*); Dysphagia and Breathing Difficulties (see *Warnings and Precautions*); Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity (see *Warnings and Precautions*) and Urinary Retention in Patients treated for Bladder Dysfunction (see *Warnings and Precautions*).

Glabellar Lines, Lateral Canthal Lines, and Forehead Lines

The most frequently reported adverse reaction following injection of BOTOX® Cosmetic for glabellar lines was eyelid ptosis (3%). The most frequently reported adverse reaction following injection of BOTOX® Cosmetic for lateral canthal lines was eyelid edema (1%). The most frequently reported adverse reactions following injection of BOTOX® Cosmetic for forehead lines with glabellar lines were headache (9%), brow ptosis (2%) and eyelid ptosis (2%).

Post Marketing Experience

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors

including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Co-administration of BOTOX[®] or BOTOX[®] Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX[®] or BOTOX[®] Cosmetic may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX[®] or BOTOX[®] Cosmetic.

USE IN SPECIFIC POPULATIONS

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX[®] Cosmetic or BOTOX[®] in pregnant women. There are no data on the presence of BOTOX[®] Cosmetic in human or animal milk, the effects on the breastfed child, or the effects on milk production.