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2 **BOTOX® (Botulinum Toxin Type A)**  
3 **Purified Neurotoxin complex**  
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Manufactured by:  
Allergan Pharmaceuticals Ireland  
a subsidiary of  
Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612

6 **DESCRIPTION: BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex** is a sterile,  
7 vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium*  
8 *botulinum* type A grown in a medium containing casein hydrolysate, glucose and yeast extract. It is  
9 purified from the culture solution by dialysis and a series of acid precipitations to a complex  
10 consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile  
11 sodium chloride solution containing Albumin (Human) and is sterile filtered (0.2 microns) prior to  
12 filling and vacuum-drying.

13 One Unit of **BOTOX®** corresponds to the calculated median intraperitoneal lethal dose (LD<sub>50</sub>) in  
14 mice. The method utilized for performing the assay is specific to Allergan's product, **BOTOX®**.  
15 Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for  
16 the various mouse LD<sub>50</sub> assays, Units of biological activity of **BOTOX®** cannot be compared to nor  
17 converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay  
18 method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes  
19 precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific  
20 activity of **BOTOX®** is approximately 20 Units/nanogram of neurotoxin protein complex.

21 Each vial of **BOTOX®** contains 100 Units (U) of *Clostridium botulinum* type A neurotoxin complex,  
22 0.5 milligrams of Albumin (Human), and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried  
23 form without a preservative.

24 **CLINICAL PHARMACOLOGY: BOTOX®** blocks neuromuscular transmission by binding to  
25 acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting  
26 the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein  
27 integral to the successful docking and release of acetylcholine from vesicles situated within nerve  
28 endings.

29 When injected intramuscularly at therapeutic doses, **BOTOX®** produces partial chemical denervation  
30 of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may  
31 atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There  
32 is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation  
33 produced by **BOTOX®**.

34 When injected intradermally, **BOTOX®** produces temporary chemical denervation of the sweat gland  
35 resulting in local reduction in sweating.

36 **Pharmacokinetics**

37 Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels  
38 following IM or intradermal injection at the recommended doses. The recommended quantities of  
39 neurotoxin administered at each treatment session are not expected to result in systemic, overt distant  
40 clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However,

41 sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of  
42 botulinum toxins appropriate to produce clinically observable local muscle weakness.

43 **Clinical Studies:**

44 **Cervical Dystonia:**

45 A phase 3 randomized, multi-center, double blind, placebo-controlled study of the treatment of  
46 cervical dystonia was conducted.<sup>1</sup> This study enrolled adult patients with cervical dystonia and a  
47 history of having received **BOTOX®** in an open label manner with perceived good response and  
48 tolerable side effects. Patients were excluded if they had previously received surgical or other  
49 denervation treatment for their symptoms or had a known history of neuromuscular disorder.  
50 Subjects participated in an open label enrichment period where they received their previously  
51 employed dose of **BOTOX®**. Only patients who were again perceived as showing a response were  
52 advanced to the randomized evaluation period. The muscles in which the blinded study agent  
53 injections were to be administered were determined on an individual patient basis.

54

55 There were 214 subjects evaluated for the open label period, of which 170 progressed into the  
56 randomized, blinded treatment period (88 in the **BOTOX**<sup>®</sup> group, 82 in the placebo group). Patient  
57 evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a  
58 dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS)  
59 and an increase in the percentage of patients showing any improvement on the Physicians Global  
60 Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of  
61 abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5  
62 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of  
63 scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category  
64 scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from -4  
65 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline  
66 and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was  
67 evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4  
68 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and  
69 the pain-related secondary endpoints are shown in Table 1.

70

71 *Table 1: Efficacy Outcomes of The Phase 3 Cervical Dystonia Study*  
 72 *(Group Means)*

	Placebo N=82	<b>BOTOX</b> <sup>®</sup> N=88	95% CI on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3) <sup>[a,b]</sup>
Percentage Patients with Any Improvement on Physicians Global Assessment	31%	51%	(5%, 34%) <sup>[a]</sup>
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2) <sup>[c]</sup>
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0) <sup>[c]</sup>

73 [a] Confidence intervals are constructed from the analysis of covariance table with treatment and  
 74 investigational site as main effects, and baseline CDSS as a covariate.

75 [b] These values represent the prospectively planned method for missing data imputation and  
 76 statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of  
 77 no difference between groups and the p-value was less than 0.05. These analyses included several  
 78 alternative missing data imputation methods and non-parametric statistical tests.

79 [c] Confidence intervals are based on the t-distribution

80 Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial  
81 response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory  
82 analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female  
83 patients may receive somewhat greater amounts than male patients. There is a consistent treatment-  
84 associated effect between subsets greater than and less than age 65 (see also **PRECAUTIONS:**  
85 **Geriatrics**). There were too few non-Caucasian patients enrolled to draw any conclusions regarding  
86 relative efficacy in racial subsets.

87 There were several randomized studies conducted prior to the phase 3 study which were supportive  
88 but not adequately designed to assess or quantitatively estimate the efficacy of **BOTOX®**.

89 In the phase 3 study the median total **BOTOX®** dose in patients randomized to receive **BOTOX®**  
90 (n=88) was 236 Units, with 25<sup>th</sup> to 75<sup>th</sup> percentile ranges of 198 to 300 Units. Of these 88 patients,  
91 most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5  
92 muscles and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown  
93 in Table 2. The total dose and muscles selected were tailored to meet individual patient needs.

94 *Table 2: Number of Patients Treated Per Muscle And*  
 95 *Fraction Of Total Dose Injected Into Involved Muscles*

<b>Muscle*</b>	<b>Number of Patients Treated in this Muscle (N=88)</b>	<b>Mean % Dose per Muscle</b>	<b>Mid-Range of % Dose per Muscle*</b>
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

96 \*The mid-range of dose is calculated as the 25<sup>th</sup> to 75<sup>th</sup> percentiles.

97 NOTE: There were 16 patients who had additional muscles injected.

98 Primary Axillary Hyperhidrosis:

99 The efficacy and safety of **BOTOX**® for the treatment of primary axillary hyperhidrosis were  
100 evaluated in two randomized, multi-center, double-blind, placebo-controlled studies.

101

102 Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a  
103 Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50mg of sweat in each axilla  
104 at rest over 5 minutes. HDSS is a 4-point scale with 1= “underarm sweating is never noticeable and  
105 never interferes with my daily activities”; to 4 = “underarm sweating is intolerable and always  
106 interferes with my daily activities”. A total of 322 patients were randomized in a 1:1:1 ratio to  
107 treatment in both axillae with either 50 Units of **BOTOX**®, 75 Units of **BOTOX**®, or placebo.  
108 Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-  
109 injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50mg sweat  
110 in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

111 Study responders were defined as patients who showed at least a 2-grade improvement from baseline  
112 value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response  
113 after their first treatment session and did not receive re-treatment during the study. Spontaneous  
114 resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a  
115 period of 5 minutes (gravimetric measurement). Sweat production responders were those patients  
116 who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

117 In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50%  
118 to 54% and from 46 % to 50% for a score of 4. The median amount of sweat production (averaged for  
119 each axilla) was 102g, 123 g, and 114 g for the placebo, 50 Units and 75 Units groups respectively.



120 The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based  
 121 on a >50% decrease from baseline in axillary sweat production was greater in both **BOTOX®** groups  
 122 than in the placebo group (p < 0.001), but was not significantly different between the 2 **BOTOX®**  
 123 doses (See Table 3).

124 *Table 3: Study 1. Study Outcomes*

Treatment Response	Botox 50 Units N = 104	Botox 75 Units N=110	Placebo N= 108	Botox 50- placebo (95% CI)	Botox 75- placebo (95% CI)
HDSS Score change ≥2 % (n) <sup>a</sup>	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

125 [a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment  
 126 sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

127 Duration of response was calculated as the number of days between injection and the date of the first  
128 visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response  
129 following the first treatment in BOTOX®-treated patients with either dose was 201 days. Among  
130 those who received a second BOTOX® injection, the median duration of response was similar to that  
131 observed after the first treatment.

132 In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either  
133 50 Units of BOTOX® (n=242) or placebo (n=78). Treatment responders were defined as subjects  
134 showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric  
135 measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91%  
136 (219/242) in the BOTOX® group and 36% (28/78) in the placebo group,  $p < 0.001$ . The difference in  
137 percentage of responders between BOTOX® and placebo was 55% (95% CI = 43.3, 65.9).

#### 138 Blepharospasm:

139 Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an  
140 open label uncontrolled study, 27 patients with essential blepharospasm were injected with 2.0 Units  
141 of BOTOX® at each of six sites on each side. One patient had not received any prior treatment.  
142 Twenty-six of the patients had not responded to therapy with benztropine mesylate, clonazepam  
143 and/or baclofen. Three of the 26 patients continued to experience spasms following muscle stripping  
144 surgery. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48  
145 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one  
146 patient reported mild improvement but remained functionally impaired.<sup>2</sup>

147 In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-  
148 controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo  
149 group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved  
150 by 61%, and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a  
151 mean of 12.5 weeks.<sup>3</sup>

152 One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open  
153 label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed  
154 intensity of lid spasm, lasting an average of 12.5 weeks prior to the need for re-treatment.<sup>4</sup>

#### 155 **Strabismus:**

156 It is postulated that when used for the treatment of strabismus, the administration of **BOTOX®**  
157 affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding  
158 shortening of the muscle's antagonist; it was on the basis of this hypothesis that clinical studies were  
159 conducted. Six hundred seventy-seven patients with strabismus treated with one or more injections of  
160 **BOTOX®** were evaluated in an open label trial. Fifty-five percent of these patients improved to an  
161 alignment of 10 prism diopters or less when evaluated six months or more following injection.<sup>5</sup>

162 These results are consistent with results from additional open label trials which were conducted for  
163 this indication.<sup>4</sup>

#### 164 **INDICATIONS AND USAGE:**

165 **BOTOX®** is indicated for the treatment of cervical dystonia in adults to decrease the severity of  
166 abnormal head position and neck pain associated with cervical dystonia.

167 **BOTOX®** is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately  
168 managed with topical agents.

169 **BOTOX®** is indicated for the treatment of strabismus and blepharospasm associated with dystonia,  
170 including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and  
171 above.

172 The efficacy of **BOTOX®** treatment in deviations over 50 prism diopters, in restrictive strabismus, in  
173 Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical  
174 over-recession of the antagonist has not been established. **BOTOX®** is ineffective in chronic  
175 paralytic strabismus except when used in conjunction with surgical repair to reduce antagonist  
176 contracture.

177 **CONTRAINDICATIONS:** **BOTOX®** is contraindicated in the presence of infection at the proposed  
178 injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

179 **WARNINGS:**

180 The recommended dosage and frequency of administration for **BOTOX®** should not be exceeded.

181 Risks resulting from administration at higher dosages are not known.

182 **Hypersensitivity Reactions**

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

188 **Pre-Existing Neuromuscular Disorders**

189 Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor  
190 neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton  
191 syndrome) should only receive **BOTOX®** with caution. Patients with neuromuscular disorders may  
192 be at increased risk of clinically significant systemic effects including severe dysphagia and  
193 respiratory compromise from typical doses of **BOTOX®**. Published medical literature has reported  
194 rare cases of administration of a botulinum toxin to patients with known or unrecognized  
195 neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of  
196 typical clinical doses. In some of these cases, dysphagia has lasted several months and required  
197 placement of a gastric feeding tube.

198 **Dysphagia**

199 Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients  
200 with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough  
201 to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to  
202 the finding of dysphagia a patient developed aspiration pneumonia and died.

203 **Human Albumin**

204 This product contains albumin, a derivative of human blood. Based on effective donor screening and  
205 product manufacturing processes, it carries an extremely remote risk for transmission of viral  
206 diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered  
207 extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for  
208 albumin.

209 **PRECAUTIONS:**

210 The safe and effective use of **BOTOX®** depends upon proper storage of the product, selection of the  
211 correct dose, and proper reconstitution and administration techniques. Physicians administering  
212 **BOTOX®** must understand the relevant neuromuscular and/or orbital anatomy of the area involved  
213 and any alterations to the anatomy due to prior surgical procedures. An understanding of standard  
214 electromyographic techniques is also required for treatment of strabismus and may be useful for the  
215 treatment of cervical dystonia.

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

218 **Cervical Dystonia:**

219 Patients with smaller neck muscle mass and patients who require bilateral injections into the  
220 sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose  
221 injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into  
222 the levator scapulae may be associated with an increased risk of upper respiratory infection and  
223 dysphagia.

224 **Primary Axillary Hyperhidrosis:**

225 Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g. hyperthyroidism) to  
226 avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the  
227 underlying disease. The safety and effectiveness of **BOTOX**® for hyperhidrosis in other body areas  
228 have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who  
229 receive **BOTOX**® for palmar hyperhidrosis and facial hyperhidrosis, respectively.

230 **Blepharospasm:**

231 Reduced blinking from **BOTOX**® injection of the orbicularis muscle can lead to corneal exposure,  
232 persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders.  
233 One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of  
234 this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of  
235 injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect  
236 should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or  
237 closure of the eye by patching or other means.

238 **Strabismus:**

239 During the administration of **BOTOX**® for the treatment of strabismus, retrobulbar hemorrhages  
240 sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It  
241 is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe)  
242 penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be  
243 available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation,  
244 double vision or past pointing. Covering the affected eye may alleviate these symptoms.

245 **Information for Patients:**

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

248 Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia,  
249 which is typically mild to moderate, but could be severe. Rare consequences of severe dysphagia  
250 include aspiration, dyspnea, pneumonia, and the need to reestablish an airway.

251 As with any treatment with the potential to allow previously sedentary patients to resume activities,  
252 the sedentary patient should be cautioned to resume activity gradually following the administration of  
253 **BOTOX**®.

254 **Drug Interactions:**

255 Co-administration of **BOTOX**® and aminoglycosides or other agents interfering with neuromuscular  
256 transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the  
257 toxin may be potentiated.



258 The effect of administering different botulinum neurotoxin serotypes at the same time or within  
259 several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by  
260 administration of another botulinum toxin prior to the resolution of the effects of a previously  
261 administered botulinum toxin.

262 **Pregnancy:** Pregnancy Category C

263 When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the  
264 developmental NOEL of **BOTOX®** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with  
265 reductions in fetal body weights and/or delayed ossification which may be reversible.

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

270 There are no adequate and well-controlled studies of **BOTOX®** in pregnant women. Because animal  
271 reproductive studies are not always predictive of human response, **BOTOX®** should be administered  
272 during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is  
273 used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should  
274 be apprised of the potential risks, including abortion or fetal malformations which have been observed  
275 in rabbits.

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

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

282 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many  
283 drugs are excreted in human milk, caution should be exercised when **BOTOX®** is administered to a  
284 nursing woman.

285 **Pediatric Use:** Safety and effectiveness in children below the age of 12 have not been established  
286 for blepharospasm or strabismus, below the age of 16 for cervical dystonia or 18 for hyperhidrosis.

287 **Geriatric Use:** Clinical studies of **BOTOX®** did not include sufficient numbers of subjects aged 65  
288 and over to determine whether they respond differently from younger subjects. Other reported  
289 clinical experience has not identified differences in responses between the elderly and younger  
290 patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose  
291 selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,  
292 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant  
293 disease or other drug therapy.

294 **ADVERSE REACTIONS:**

295 **General:**

296 There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia,  
297 and/or other significant debility or anaphylaxis, after treatment with botulinum toxin.

298 There have also been rare reports of adverse events involving the cardiovascular system, including  
299 arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk  
300 factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin  
301 injection has not been established.

302 The following events have been reported since the drug has been marketed and a causal relationship  
303 to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and  
304 psoriasiform eruption), pruritus, and allergic reaction.

305 In general, adverse events occur within the first week following injection of **BOTOX®** and while  
306 generally transient may have a duration of several months. Localized pain, tenderness and/or bruising  
307 may be associated with the injection. Local weakness of the injected muscle(s) represents the  
308 expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may  
309 also occur due to spread of toxin.

310 **Cervical Dystonia:**

311 In cervical dystonia patients evaluated for safety in double-blind and open-label studies following  
312 injection of **BOTOX®**, the most frequently reported adverse reactions were dysphagia (19%), upper  
313 respiratory infection (12%), neck pain (11%), and headache (11%).<sup>7</sup>

314 Other events reported in 2-10% of patients in any one study in decreasing order of incidence include:  
315 increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site,  
316 asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia,  
317 ptosis, and dyspnea have been reported rarely.

318 Dysphagia and symptomatic general weakness may be attributable to an extension of the  
319 pharmacology of **BOTOX®** resulting from the spread of the toxin outside the injected muscles.

320 The most common severe adverse event associated with the use of **BOTOX®** injection in patients  
321 with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea. (See  
322 **Warnings**). Most dysphagia is reported as mild or moderate in severity. However, it may rarely be  
323 associated with more severe signs and symptoms (See **Warnings**).

324 Additionally, reports in the literature include a case of a female patient who developed brachial  
325 plexopathy two days after injection of 120 Units of **BOTOX®** for the treatment of cervical dystonia,  
326 and reports of dysphonia in patients who have been treated for cervical dystonia.

#### 327 **Primary Axillary Hyperhidrosis:**

328 The most frequently reported adverse events (3 - 10% of patients) following injection of **BOTOX®**  
329 in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection,  
330 pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

331 The data reflect 346 patients exposed to **BOTOX®** 50 Units and 110 patients exposed to **BOTOX®**  
332 75 Units in each axilla.

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

336 **Blepharospasm:**

337 In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3  
338 to 5 sites) of the currently manufactured **BOTOX®**, the most frequently reported treatment-related  
339 adverse reactions were ptosis (20.8%), superficial punctate keratitis (6.3%) and eye dryness (6.3%).<sup>8</sup>

340 In this study, the rate for ptosis in the current **BOTOX®** treated group (20.8% of patients) was  
341 significantly higher than the original **BOTOX®** treated group (4.0% of patients) ( $p=0.014\%$ ). All of  
342 these events were mild or moderate except for one case of ptosis which was rated severe.

343 Other events reported in prior clinical studies in decreasing order of incidence include: irritation,  
344 tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia and entropion, diffuse skin rash  
345 and local swelling of the eyelid skin lasting for several days following eyelid injection.

346 In two cases of VII nerve disorder (one case of an aphakic eye), reduced blinking from **BOTOX®**  
347 injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and  
348 corneal ulceration. Perforation occurred in the aphakic eye and required corneal grafting.

349 A report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for  
350 blepharospasm was received, with recovery four months later after laser iridotomy and  
351 trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also  
352 been reported after treatment of blepharospasm.

353 **Strabismus:**

354 Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviation,  
355 especially with higher doses of **BOTOX®**. The incidence rates of these adverse effects in 2058  
356 adults who received a total of 3650 injections for horizontal strabismus are 15.7% and 16.9%,  
357 respectively.<sup>4</sup>

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

360 The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus  
361 injection.

362 Ptosis (0.3%) and vertical deviation greater than two prism diopters (2.1%) were reported to persist  
363 for over six months in a larger series of 5587 injections of horizontal muscles in 3104 patients.

364 In these patients, the injection procedure itself caused nine scleral perforations. A vitreous  
365 hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss occurred in  
366 any case. Sixteen retrobulbar hemorrhages occurred without visual loss. Decompression of the orbit  
367 after five minutes was done to restore retinal circulation in one case. Five eyes had pupillary change  
368 consistent with ciliary ganglion damage (Adie's pupil).

369 One patient developed anterior segment ischemia after receiving **BOTOX®** injection into the medial  
370 rectus muscle under direct visualization for esotropia.

371 **Immunogenicity:**

372 Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of  
373 **BOTOX®** treatment by inactivating the biological activity of the toxin. The rate of formation of  
374 neutralizing antibodies in patients receiving **BOTOX®** has not been well studied.

375

376 In the phase 3 cervical dystonia study<sup>1</sup> that enrolled only patients with a history of receiving  
377 **BOTOX®** for multiple treatment sessions, at study entry there were 192 patients with antibody assay  
378 results, of whom 33 (17%) had a positive assay for neutralizing activity. There were 96 patients in  
379 the randomized period of the phase 3 study with valid assays at both study entry and end and who  
380 were neutralizing activity negative at entry. Of these 96, 2 patients (2%) converted to positive for  
381 neutralizing activity. Both of these converting patients were among the 52 who had received two  
382 **BOTOX®** treatments between the two assays; none were in the group randomized to placebo in the  
383 controlled comparison period of the study.

384

385 In the randomized period of the cervical dystonia study, patients in the **BOTOX**<sup>®</sup> group whose  
386 baseline assays were neutralizing antibody negative showed improvements on CDSS (n=64, mean  
387 CDSS change -2.1) while patients whose baseline assays were neutralizing antibody positive did not  
388 (n=14, mean CDSS change +1.1). However, in uncontrolled studies there are also individual patients  
389 who are perceived as continuing to respond to treatments despite the presence of neutralizing activity.  
390 Not all patients who become non-responsive to **BOTOX**<sup>®</sup> after an initial period of clinical response  
391 have demonstrable levels of neutralizing activity.

392 One patient among the 445 hyperhidrosis patients with analyzed specimens showed the presence of  
393 neutralizing antibodies.

394 The data reflect the patients whose test results were considered positive or negative for neutralizing  
395 activity to **BOTOX**<sup>®</sup> in a mouse protection assay. The results of these tests are highly dependent on  
396 the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing  
397 activity in an assay may be influenced by several factors including sample handling, concomitant  
398 medications and underlying disease. For these reasons, comparison of the incidence of neutralizing  
399 activity to **BOTOX**<sup>®</sup> with the incidence reported to other products may be misleading.

400

401 The critical factors for neutralizing antibody formation have not been well characterized. The results  
402 from some studies suggest that **BOTOX**<sup>®</sup> injections at more frequent intervals or at higher doses  
403 may lead to greater incidence of antibody formation. The potential for antibody formation may be  
404 minimized by injecting with the lowest effective dose given at the longest feasible intervals between  
405 injections.



406

407 **OVERDOSAGE:**

408 Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental  
409 injection or oral ingestion occur, the person should be medically supervised for up to several weeks  
410 for signs or symptoms of systemic weakness or muscle paralysis.

411 An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. In the  
412 event of an overdose or injection into the wrong muscle, immediately contact Allergan for additional  
413 information at (800) 433-8871 from 8:00 a.m. to 4:00 p.m. Pacific Time, or at (714) 246-5954 for a  
414 recorded message at other times. The antitoxin will not reverse any botulinum toxin induced muscle  
415 weakness effects already apparent by the time of antitoxin administration.

416 **DOSAGE AND ADMINISTRATION:**

417 **BOTOX®** is supplied in a single use vial. Because the product and diluent do not contain a  
418 preservative, once opened and reconstituted, store in a refrigerator and use within four hours. Discard  
419 any remaining solution. Do not freeze reconstituted **BOTOX®**.

420 **BOTOX®** is to be reconstituted with sterile, non-preserved saline prior to intramuscular injection.

421 **General:**

422 An injection of **BOTOX®** is prepared by drawing into an appropriately sized sterile syringe an  
423 amount of the properly reconstituted toxin (see Dilution Table) slightly greater than the intended  
424 dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate  
425 injection needle. Patency of the needle should be confirmed. A new, sterile, needle and syringe  
426 should be used to enter the vial on each occasion for removal of **BOTOX®**.

427

428 The method utilized for performing the potency assay is specific to Allergan's Botulinum Toxin Type  
429 A. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols  
430 for the various potency assays, Units of biological activity of Botulinum Toxin Type A cannot be  
431 compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any  
432 other specific assay method. Therefore, differences in species sensitivities to different botulinum  
433 neurotoxin serotypes precludes extrapolation of animal dose-activity relationships to human dose  
434 relationships.

435

436 **Cervical Dystonia:**

437 The phase 3 study enrolled patients who had extended histories of receiving and tolerating **BOTOX®**  
438 injections, with prior individualized adjustment of dose. The mean **BOTOX®** dose administered to  
439 patients in the phase 3 study was 236 Units (25<sup>th</sup> to 75<sup>th</sup> percentile range 198 Units to 300 Units). The  
440 **BOTOX®** dose was divided among the affected muscles (see Clinical Studies: Cervical Dystonia).  
441 Dosing in initial and sequential treatment sessions should be tailored to the individual patient based  
442 on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response  
443 and adverse event history.

444 The initial dose for a patient without prior use of **BOTOX**® should be at a lower dose, with  
445 subsequent dosing adjusted based on individual response. Limiting the total dose injected into the  
446 sternocleidomastoid muscles to 100 Units or less may decrease the occurrence of dysphagia (see  
447 Precautions: Cervical Dystonia).

448 A 25, 27 or 30 gauge needle may be used for superficial muscles, and a longer 22 gauge needle may  
449 be used for deeper musculature. Localization of the involved muscles with electromyographic  
450 guidance may be useful.

451 Clinical improvement generally begins within the first two weeks after injection with maximum  
452 clinical benefit at approximately six weeks post-injection. In the phase 3 study most subjects were  
453 observed to have returned to pre-treatment status by 3 months post-treatment.

454 **Primary Axillary Hyperhidrosis**

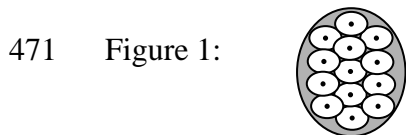
455 The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined  
456 using standard staining techniques, e.g., Minor's Iodine-Starch Test. **BOTOX®** is reconstituted with  
457 0.9% non-preserved sterile saline (100 Units/4 mL). Using a 30 gauge needle, 50 Units of **BOTOX®**  
458 (2mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple  
459 sites (10-15) approximately 1-2 cm apart.

460 Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous  
461 injection diminishes.

462 **Instructions for the Minor's Iodine Starch Test Procedure**

463 Patients should shave underarms and abstain from use of over-the-counter deodorants or  
464 antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise,  
465 hot drinks, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then  
466 immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with  
467 starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep  
468 blue-black color over approximately 10 minutes.

469 Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area  
470 of no effect, the injection sites should be evenly spaced as shown in Figure 1:



472 Each dose is injected to a depth of approximately 2mm and at a 45° angle to the skin surface with the  
473 bevel side up to minimize leakage and to ensure the injections remain intradermal.

474 If injection sites are marked in ink do not inject **BOTOX**<sup>®</sup> directly through the ink mark to avoid a  
475 permanent tattoo effect.

476 **Blepharospasm:**

477 For blepharospasm, reconstituted **BOTOX**<sup>®</sup> (see Dilution Table) is injected using a sterile, 27 - 30  
478 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 - 2.5 Units  
479 (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis  
480 oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding  
481 injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding  
482 medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the  
483 complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented  
484 by applying pressure at the injection site immediately after the injection.

485 In general, the initial effect of the injections is seen within three days and reaches a peak at one to two  
486 weeks post-treatment. Each treatment lasts approximately three months, following which the  
487 procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if  
488 the response from the initial treatment is considered insufficient-usually defined as an effect that does  
489 not last longer than two months. However there appears to be little benefit obtainable from injecting  
490 more than 5.0 Units per site. Some tolerance may be found when **BOTOX**<sup>®</sup> is used in treating  
491 blepharospasm if treatments are given any more frequently than every three months, and is rare to  
492 have the effect be permanent.

493 The cumulative dose of **BOTOX**<sup>®</sup> treatment in a 30-day period should not exceed 200 Units.

494 **Strabismus:**

495 **BOTOX®** is intended for injection into extraocular muscles utilizing the electrical activity recorded  
496 from the tip of the injection needle as a guide to placement within the target muscle. Injection  
497 without surgical exposure or electromyographic guidance should not be attempted. Physicians should  
498 be familiar with electromyographic technique.

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

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

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

510 I. Initial doses in Units. Use the lower listed doses for treatment of small deviations. Use the larger  
511 doses only for large deviations.

512 A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 - 2.5  
513 Units in any one muscle.

514 B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 - 5.0 Units in any one  
515 muscle.

516 C. For persistent VI nerve palsy of one month or longer duration: 1.25 - 2.5 Units in the medial  
517 rectus muscle.

518 II. Subsequent doses for residual or recurrent strabismus.

519 A. It is recommended that patients be re-examined 7-14 days after each injection to assess the  
520 effect of that dose.

521 B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections  
522 should receive a dose comparable to the initial dose.

523 C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be  
524 increased up to two-fold compared to the previously administered dose.

525 D. Subsequent injections should not be administered until the effects of the previous dose have  
526 dissipated as evidenced by substantial function in the injected and adjacent muscles.

527 E. The maximum recommended dose as a single injection for any one muscle is 25 Units.

528 **Dilution Technique:**

529 Prior to injection, reconstitute vacuum-dried **BOTOX®**, with sterile normal saline **without** a  
530 preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper  
531 amount of diluent in the appropriate size syringe, and slowly inject the diluent into the vial. Discard  
532 the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX®** with the saline by  
533 rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX®**  
534 should be administered within four hours after reconstitution.

535 During this time period, reconstituted **BOTOX®** should be stored in a refrigerator (2° to 8°C).

536 Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter. Parenteral drug  
537 products should be inspected visually for particulate matter and discoloration prior to administration  
538 and whenever the solution and the container permit.

539 *Dilution Table*

<b>Diluent Added (0.9% Sodium Chloride Injection)</b>	<b>Resulting dose Units per 0.1 mL</b>
1.0 mL	10.0 Units
2.0 mL	5.0 Units
4.0 mL	2.5 Units
8.0 mL	1.25 Units

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

543 **HOW SUPPLIED:** **BOTOX**® is supplied in a single use vial. Each vial contains 100 Units of  
544 vacuum-dried *Clostridium botulinum* type A neurotoxin complex. NDC 0023-1145-01.

545 Vials of **BOTOX**® have a holographic film on the vial label that contains the name “Allergan” within  
546 horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between  
547 your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is  
548 absent in the date/batch area.) If you do not see the lines of rainbow color or the name “Allergan”, do  
549 not use the product and contact Allergan for additional information at (800) 890-4345 from 8:00 a.m.  
550 to 4:00 p.m. Pacific time.

551 **Rx Only**

552 **Single use vial.**



553 **Storage:**

554 Unopened vials of **BOTOX**® should be stored in a refrigerator (2° to 8°C) for up to 24 months. Do  
555 not use after the expiration date on the vial. Administer **BOTOX**® within 4 hours of reconstitution;  
556 during this period reconstituted **BOTOX**® should be stored in a refrigerator (2° to 8°C).

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

558 All vials, including expired vials, or equipment used with the drug should be disposed of carefully as  
559 is done with all medical waste.

560 ® Marks owned by Allergan, Inc.

561 Revised: May 2004

562 Manufactured by: Allergan Pharmaceuticals Ireland

563 a subsidiary of: Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612

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