NAME OF THE MEDICINE

BOTOX® purified neurotoxin complex injection (50U, 100 U or 200 U)
(botulinum toxin, type A)

DESCRIPTION

Composition

Active ingredient:
Each vial of BOTOX® contains either 50 units (U), 100 units (U) or 200 units (U) of botulinum toxin, type A, as a haemagglutinin complex.

Excipients:
Human albumin: 0.25 mg for 50 U, 0.5 mg for 100 U or 1.0 mg for 200 U
Sodium chloride: 0.45 mg for 50U, 0.9 mg for 100 U or 1.8 mg for 200 U

BOTOX® (botulinum toxin type A) Neurotoxin complex is produced from the fermentation of *Clostridium botulinum* type A (Hall strain) and is purified from the culture solution as an approximately 900 kD molecular weight complex consisting of the neurotoxin and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing human serum albumin and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice, performed in a mouse potency assay. This assay method is specific to Allergan's product, BOTOX®. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, units of biological activity of BOTOX® cannot be compared to or converted into units of any other botulinum toxin activity.

PHARMACOLOGY

Pharmacodynamics

Therapeutic class: neuromuscular blocking agent.

Clostridium botulinum type A neurotoxin blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals by cleaving SNAP-25, a protein integral to the docking and release of acetylcholine from vesicles located within the nerve terminals.

After injection, there is an initial high-affinity binding of toxin to specific cell surface receptors on cholinergic nerve terminals. Bound toxin is then internalised by endocytosis, and the catalytic light chain is translocated across the vesicular membrane into the cytosol where it cleaves SNAP-25. Progressive inhibition of acetylcholine release follows and clinical signs usually manifest within 2-3 days.

Recovery after intramuscular injection takes place normally within 12 weeks. Preclinical studies have demonstrated that, new sprouts from the original preterminal axons allow for a

temporary reconnection of the neuron with the endplates. These sprouts are only partially effective and subsequently regress while the original nerve terminal at the primary neuromuscular junction becomes functional again. The relevance of these preclinical observations to the clinical condition remains to be established.

Bladder Dysfunction (Overactive Bladder and Neurogenic Detrusor Overactivity)
Due to its pharmacological mechanism of action, it is expected that BOTOX® affects the efferent pathways of detrusor activity mainly via inhibition of acetylcholine release.

Chronic Migraine
Limited nonclinical data suggest that BOTOX® may reduce sensitisation processes, but the actual mechanism of action for headache prophylaxis is not known.

Blepharospasm
The relaxing effect on muscles injected with BOTOX® is useful in reducing the excessive, abnormal contractions associated with blepharospasm. Following peri-ocular injection of BOTOX®, distant muscles show electrophysiological 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.

Typically, patients with blepharospasm show improvement lasting an average of 12.5 weeks prior to the need for re-treatment.

Strabismus
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.

Focal Spasticity in adults and children two years and older
BOTOX® treatment reduces both the objective signs and subjective symptoms of spasticity. Improvements include reduction in muscle tone, increase in range of motion, reduction in pain and a reduction of spasticity-related functional disability.

Cervical Dystonia (spasmodic torticollis)
When injected into neck muscles, BOTOX® reduces both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements may include reduced pain/discomfort, reduced head rotation, reduced shoulder elevation, decreased size and strength of hypertrophic muscles, and functional disability improvement. Based on the results of early publications in naïve patients, 40 to 58% of patients with cervical dystonia respond with a significant improvement in their symptoms after initial treatment with BOTOX®. Among patients who have previously benefited from BOTOX® injection for cervical dystonia, approximately 91% can expect improvement for any given treatment period based on patient withdrawal data in a recent trial.

Primary Hyperhidrosis of the Axillae
The proposed mechanism of action of BOTOX® in hyperhidrosis is the inhibition of cholinergically driven excessive sweating, by locally blocking the autonomic sympathetic cholinergic nerve fibres innervating sweat glands. This is achieved by injecting the toxin in the vicinity of the sweat glands, which are located within the dermis of the skin. Injections

for this indication must therefore be given intradermally. Hyperhidrosis is typically treated by multiple intradermal injections given in a grid-like pattern over the affected area. The objective of treatment is to reduce sweating to a physiologically normal level which patients find tolerable. Anhidrosis is not the target.

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

Spasmodic Dysphonia
Spasmodic dysphonia is a focal laryngeal dystonia with task specific spasms of the vocal cords seriously interfering with communication. Approximately 90% of the patients have adductor spasmodic dysphonia with spasms of the adductor muscles including thyroarytenoid, lateral cricoarytenoid and interarytenoid muscles. About 10% of patients have abductor spasmodic dysphonia with spasms of the abductors of the vocal cords, in particular the posterior cricoarytenoid muscles. Many studies have shown that at least 90% of patients with adductor spasmodic dysphonia obtain a satisfactory or better result with BOTOX® injections. Treatment of abductor spasmodic dysphonia is more technically difficult and results are less satisfactory, but with a tailored approach most patients still obtain satisfactory improvement with BOTOX® injections.

Glabellar Lines
Glabellar lines are secondary to relative overactivity (or hyperfunctioning) of the muscles associated with frowning. When injected into the corrugator and/or procerus muscles, BOTOX® weakens the overactive underlying muscle contraction, decreasing the severity of the glabellar lines and improving appearance. In controlled clinical trials, onset of action was rapid (effect of BOTOX® was apparent at the first assessment timepoint of 7 days) and lasted at least 4 months for many subjects.

Crow's Feet
Crow's feet are well established, deep, radiating, horizontal and oblique furrows at the temporal aspect of each eye and are the direct result of the contraction of the lateral fibers of the orbicularis oculi muscles. In controlled clinical trials, injections of BOTOX® into the lateral orbital area resulted in rapid onset of action (effect of BOTOX® was apparent at the first assessment timepoint of 7 days) and reduced the severity of wrinkling in this area for up to 17 weeks.

Forehead Lines
Horizontal forehead lines are associated with chronic functional activity of the frontalis muscle. At two weeks post-injection, 84-95% of BOTOX®-treated patients were considered by investigators as treatment responders; 75-80% of patients felt they had improvement (16 or 24 U at four sites in the frontalis muscle). Higher doses of BOTOX® resulted in greater efficacy and longer duration of effect. Injections of BOTOX® reduced the severity of horizontal forehead lines for up to 24 weeks as determined by a trained observer.

Pharmacokinetics

Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the nature of this product.

Distribution in rats was studied following injection of ^{125}I-botulinum neurotoxin A complex into the gastrocnemius muscle. Radioactivity associated with the toxin complex was mostly retained at the injection site, declining with a half-life of approximately 10 hours. Radioactivity detected in other locations (plasma, muscle, thyroid, skin) was mainly associated with probable breakdown products, indicating minimal systemic exposure to toxin. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. The toxin is probably metabolised by proteases and the molecular components cycled through normal metabolic pathways.

CLINICAL TRIALS – Therapeutic Indications

Overactive Bladder

Two double-blind, placebo-controlled, randomised, multi-center, 24-week Phase 3 clinical studies were conducted in patients with OAB with symptoms of urinary incontinence, urgency, and frequency. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX® (n=557), or placebo (n=548). Patients had to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days, a negative urine dipstick at randomisation and to be willing to use Clean Intermittent Catheterisation (CIC) if deemed necessary by the investigator. Patients were excluded if they had other urological conditions that could confound the studies such as: OAB secondary to any known neurological reason, a predominance of stress incontinence, anticholinergic treatment or any other therapies for OAB within the 7 days prior to baseline , already using CIC or an in-dwelling catheter, previous botulinum toxin therapy within the previous 12 weeks or immunisation for any botulinum toxin serotype, significant pelvic or urological abnormalities other than OAB or post-void residual (PVR) urine volume > 100 ml at screening among others.

Baseline characteristics were similar between the treatment groups in both studies: pooled mean age 60 years, 87.8% female, 90.9% Caucasian, 13.7% diabetic patients, mean 5.4 daily episodes of urinary incontinence, mean 11.7 daily episodes of micturition and mean 8.6 daily average urgency episodes.

In both studies, significant improvements compared to placebo in the change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX® (100 U) at the primary time point of week 12, including the proportion of dry patients. Using the Treatment Benefit Scale, the proportion of patients reporting a positive treatment response (their condition has been 'greatly improved' or 'improved') was significantly greater in the BOTOX® group compared to the placebo group in both studies. Significant improvements compared to placebo were also observed for the daily frequency of micturition, urgency, and nocturia episodes. Volume voided per micturition was also significantly higher. Significant improvements were observed in all OAB symptoms from week 2.

BOTOX® treatment was associated with significant improvements over placebo in health-related quality of life as measured by the Incontinence Quality of Life (I-QOL) questionnaire (including avoidance and limiting behavior, psychosocial impact, and social embarrassment) and the King's Health Questionnaire (KHQ) (including incontinence impact, role limitations, social limitations, physical limitations, personal relationships, emotions, sleep/energy, and severity/coping measures).

Results from the pivotal studies are presented below:

Primary and Secondary Efficacy Variables at Baseline and Change from Baseline in Study 1 (191622-095) and Study 2 (191622-520):

	Study 1 (191622-095)			Study 2 (191622-520)		
Endpoint Timepoint	**BOTOX® 100 Units (N=280)**	**Placebo (N=277)**	**P-value; Absolute difference from placebo (95% CI)**	**BOTOX® 100 Units (N=277)**	**Placebo (N=271)**	**P-value; Absolute difference from placebo (95% CI)**
Daily Frequency of Urinary Incontinence Episodes*						
Mean Baseline	5.47	5.09		5.52	5.70	
Mean Change at Week 2	-2.85	-1.09		-2.85	-1.34	
Mean Change at Week 6	-3.05	-1.07		-3.18	-1.37	
Mean Change at Week 12[a]**	**-2.65**	**-0.87**	**< 0.001; -1.65 (-2.13, -1.17)**	**-2.95**	**-1.03**	**< 0.001; -1.91 (-2.43, -1.39)**
Proportion ~~with~~ of Positive Treatment Response using Treatment Benefit Scale (%)						
Week 2	64.5	32.6		64.2	36.8	
Week 6	66.9	34.7		69.3	30.9	
Week 12*[a]	**60.8**	**29.2**	**< 0.001; 31.8 (23.9, 39.7)**	**62.8**	**26.8**	**< 0.001; 36.0 (28.2, 43.8)**
Daily Frequency of Micturition Episodes						
Mean Baseline	11.98	11.20		12.01	11.77	
Mean Change at Week 2	-1.58	-0.79		-1.48	-0.77	
Mean Change at Week 6	-1.96	-0.98		-2.40	-0.97	
Mean Change† at Week 12[b]	**-2.15**	**-0.91**	**< 0.001 -1.04 (-1.48, -0.59)**	**-2.56**	**-0.83**	**< 0.001; -1.72 (-2.19 -1.26)**
Daily Frequency of Urgency Episodes						
Mean Baseline	8.54	7.85		9.11	8.78	
Mean Change at Week 2	-2.83	-1.34		-2.95	-1.36	
Mean Change at Week 6	-3.21	-1.45		-3.91	-1.35	
Mean Change† at Week 12[b]	**-2.93**	**-1.21**	**< 0.001; -1.51 (-2.15, -0.87)**	**-3.67**	**-1.24**	**< 0.001; -2.44 (-3.09, -1.79)**
Incontinence Quality of Life Total Score						
Mean Baseline	36.5	37.3		31.7	32.1	
Mean Change† at Week 12[bc]	**+21.9**	**+6.8**	**< 0.001; 14.9 (11.1, 18.7)**	**+23.1**	**+6.3**	**< 0.001; 16.9 (13.2, 20.6)**
King's Health Questionnaire: Role Limitation						
Mean Baseline	61.2	56.2		69.6	66.4	
Mean Change† at Week 12[bc]	**-24.3**	**-2.4**	**< 0.001; -20.6 (-25.6, -15.7)**	**-26.5**	**-5.0**	**< 0.001; -19.8 (-24.8, -14.7)**
King's Health Questionnaire: Social Limitation						
Mean Baseline	40.5	39.4		49.1	45.4	
Mean Change† at Week 12[bc]	**-17.3**	**-3.8**	**< 0.001 -13.9**	**-16.2**	**-1.3**	**< 0.001; -13.2**

			(-18.1, -9.7)			**(-17.8, -8.6)**

[*] Percentage of patients who were dry (without incontinence) at week 12 was 22.9% for the BOTOX® group and 6.5% for placebo group in Study 1 and 31.4% for the BOTOX® group and 10.3% for placebo group in Study 2. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 44.6% and 57.5% in the BOTOX® group compared to 15.2% and 28.9% in the placebo group in Study 1 and 47.3% and 63.5% in the BOTOX® group compared to 20.3% and 33.2% in the placebo group in Study 2.

[**] P-value, absolute difference in Least Squares Mean (LS Mean) and its 95% CI for daily frequency of urinary incontinence episodes at Week 12 are based on an ANCOVA model using a LOCF method with baseline value as covariate and treatment group and site as factors.

[***] P-value, absolute difference from placebo and its 95% CI for proportion of positive treatment response using TBS at Week 12 are based on Cochran-Mantel-Haenszel (CMH) test using a LOCF method with urinary urgency incontinence ≤9 or >9 episodes at baseline as a stratification factor.

[†] P-values, absolute differences from placebo in LS Mean and its 95% CI for the secondary efficacy endpoints are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and site as factors.

[a] Co-primary endpoints
[b] Secondary endpoints
[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

A total of 834 patients were evaluated in a long term extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments. In the subset of 345 patients, who had reached week 12 of treatment cycle 3, the mean reductions in daily frequency of urinary incontinence were -3.07, -3.49, and -3.49 episodes at week 12 after the first, second, and third BOTOX® 100 Unit treatments, respectively. The corresponding proportions of patients with a positive treatment response on the Treatment Benefit Scale (TBS) were 63.6%, 76.9%, and 77.3% respectively.

Only a limited number of males (n=135, 12.2%) were studied in the two phase 3 clinical studies and the results were not statistically significant for patients administered BOTOX® compared to placebo. Results for the co-primary endpoints in males are presented below and further details are located in Precautions, Overactive Bladder, Use in Males:

Co-primary Efficacy Endpoints at Baseline and Change from Baseline in Male Patients (Pooled Pivotal Studies, Placebo-controlled ITT Population)

	BOTOX® 100 Units (N=61)	**Placebo (N=74)**	**P-value**	**Absolute difference from placebo (95% CI)**
Daily Frequency of Urinary Incontinence Episodes				
Mean Baseline	5.61	4.33		
Mean Change at Week 12	-1.86	-1.23	0.612	-0.42 (-2.08, 1.23)
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)				
Week 12	40.7	25.4	0.060	15.2 (-0.8, 31.3)

The median duration of response following BOTOX® treatment, based on patient request for re-treatment was 166 days (~24 weeks). To qualify for retreatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL, and patients must have reported at least 2 urinary incontinence episodes over 3 days.

Neurogenic Detrusor Overactivity

Two double-blind, placebo-controlled, randomised, multi-centre phase 3 clinical studies were conducted in patients with urinary incontinence due to neurogenic detrusor overactivity who were either spontaneously voiding or using catheterization (indwelling catheters were not allowed). A total of 691 spinal cord injury (lesion at T1 or below) or multiple sclerosis patients (EDSS at 6.5 or below), not adequately managed with at least one anticholinergic agent, were enrolled. These patients were randomised to receive either 200 U of BOTOX® (n=227), 300 U of BOTOX® (n=223), or placebo (n=241). Both pivotal trials (191622-515 and 191622-516) were superiority studies compared to placebo. The primary endpoint was the number of episodes of urinary incontinence as recorded by patient bladder diary. Analysis of covariance was used to assess differences in efficacy between BOTOX® and placebo, with baseline value as a covariate, and treatment arm, etiology (MS or SCI), concurrent use/non-use of anticholinergics, and investigator site as factors. Baseline demographics of the pooled pivotal trial population are shown in the table below:

Baseline Demographics per Etiology in Phase 3 Studies

	MS	SCI
N (%)	381 (55.1%)	310 (44.9%)
Age, median years (range)	50.0 (22-77)	41.5 (18-77)
Male gender, N (%)	70 (18.4%)	221 (71.3%)
Using CIC, N (%)	112 (29.4%)	263 (84.8%)
Spontaneously Voiding, N (%)	265 (69.6%)	42 (13.5%)

In both phase 3 studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed favouring BOTOX® (200 U and 300 U) at the primary efficacy time point at week 6, including the percentage of dry patients. Significant improvements in some urodynamic parameters were observed, including decreases in peak detrusor pressure during the first involuntary detrusor contraction. Increases in maximum cystometric capacity were observed, but in patients who were spontaneously voiding these were offset by almost equivalent increases in post-void residual volume (please see last row of the table below).

Significant improvements in patient reported incontinence specific health-related quality of life scores as measured by the Incontinence Quality of Life questionnaire (I-QOL) (including avoidance limiting behaviour, psychosocial impact and social embarrassment) were also observed. No additional benefit of BOTOX® 300 U over 200 U was demonstrated.

Results from the pivotal studies are presents below:

Primary and Secondary Efficacy Variables at Baseline and Change from Baseline in Phase 3 Studies

	Study 1 (191622-515)			Study 2 (191622-516)		
	BOTOX® 200 U (N=135)	**Placebo (N=149)**	**p-values**	**BOTOX® 200 U (N=92)**	**Placebo (N=92)**	**p-values**
Weekly Frequency of Urinary Incontinence*						
Mean Baseline	32.3	28.3		32.5	36.7	
Mean Change at Week 2	-16.9	-8.6	p=0.008	-18.8	-9.7	p<0.001
Mean Change at Week 6[a]	**-21.0**	**-8.8**	**p<0.001**	**-21.8**	**-13.2**	**p=0.002**
Mean Change at Week 12	-20.8	-8.3	p<0.001	-20.5	-12.2	p=0.002
Maximum Cystometric Capacity (mL)						
Mean Baseline	252.3	256.0		247.3	249.4	
Mean Change at Week 6[b]	**+151.2**	**+15.5**	**p<0.001**	**+157.0**	**+6.5**	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)						
Mean Baseline	51.3	50.9		51.7	41.5	
Mean Change at Week 6[b]	**-35.1**	**-2.4**	**p<0.001**	**-28.5**	**+6.4**	**p<0.001**
Incontinence Quality of Life Total Score[c,d]						
Mean Baseline	33.95	35.06		37.46	35.72	
Mean Change at Week 6[b]	**+26.90**	**+10.81**	**p<0.001**	**+24.43**	**+11.71**	**p<0.001**
Mean Change at Week 12	+31.42	+9.05	p<0.001	+25.08	+8.56	p<0.001
Maximum Cystometric Capacity minus Post Void Residual[e]						
N	50	46		40	37	
Mean Baseline	195.1	170.1		151.2	160.0	
Mean Change at Week 6	+35.8	-36.9	-	+20.8	+16.8	-

p-values are based on an LOCF analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.

* Percentage of dry patients (without incontinence) throughout week 6 was 36.3% (200 U BOTOX® group) and 10.1% (placebo) in Study 1, and 38.0% (200 U BOTOX® group) and 7.6% (placebo) in Study 2

[a] Primary endpoint

[b] Secondary endpoints

[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

[d] In the phase 3 studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

[e] Maximum cystometric capacity (MCC) and post void residual (PVR) may not have been measured on the same day, but they were measured within the same visit window. Only patients who had MCC and PVR data at both baseline and Week 6 visits and not using CIC at baseline were analysed.

The median duration of response in the two phase 3 studies, based on patient request for re-treatment, was 256-295 days (36-42 weeks) for the 200 U dose group compared to 92 days (13 weeks) with placebo.

Placebo recipients crossed over to active therapy for subsequent treatment cycles so there are no placebo-controlled data beyond the first treatment cycle. For all efficacy endpoints, patients receiving a second treatment experienced a broadly similar response. Data beyond two intradetrusor treatments are limited.

Chronic Migraine

BOTOX® was evaluated in two multi-national, multi-centre 56-week studies that included a 24-week, 2 injection cycle, double-blind phase comparing BOTOX® to placebo (saline), followed by a 32-week, 3 injection cycle, open-label phase. A total of 1,384 chronic migraine adults who had either never received or were not using any concurrent headache prophylaxis during a 28-day baseline, had ≥ 15 headache days, with 50% being migraine/probable migraine, and ≥ 4 headache episodes were studied in two phase 3 clinical trials. These patients had a mean duration of chronic migraine for 19.2 ± 12.56 years, and during the 28-day baseline 906 (65.5%) patients were and 478 (34.5%) patients were not overusing acute headache pain medications. These patients were randomised to placebo (saline) or to 155 U - 195 U BOTOX® injections every 12 weeks; maximum 5 injection cycles. During the trial, patients were allowed to use acute headache treatments. BOTOX® treatment demonstrated statistically significant ($p<0.001$) and clinically meaningful improvements from baseline compared to placebo (saline) for 50% reduction in headache days, mean frequency of moderate/severe headache days and total cumulative hours of headache on headache days (see Tables 1, 2, 3 and 4). Results of the Headache Impact Test (HIT-6) and Migraine-Specific Quality of Life (MSQ) questionnaires indicated BOTOX® had a sustained duration of action and improved functioning, vitality, psychological distress and overall quality of life (refer to Tables 1, 2, 3 and 4).

Table 1: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies

Efficacy per 28 days	**Pooled Studies 191622-079 & 191622-080**		
	BOTOX® (N=688)	Placebo (saline) (N=696)	p- value
Mean change from baseline in frequency of headache days [a]	-8.4	-6.6	<0.001
Mean change from baseline in frequency of migraine/probable migraine days [a]	-8.2	-6.2	<0.001
Mean change from baseline in number of moderate/severe headache days [a]	-7.7	-5.8	<0.001
Mean change from baseline in total cumulative hours of headache on headache days [a]	-119.73	-80.49	<0.001
Mean change from baseline in frequency of headache episodes [a]	-5.2	-4.9	0.009
Decrease from baseline in 50% or more headache days [a]	47.1%	35.1%	<0.001
Proportion of patients with severe HIT-6 category scores [b]	67.6%	78.2%	<0.001
Total HIT-6 scores [b]	-4.8	-2.4	<0.001
Mean change from baseline in MSQ scores [b] Role function- Restrictive	-17.0	-8.6	<0.001

Role function- Preventative	-13.1	-6.4	<0.001
Role function- Emotional Function	-17.9	-9.5	<0.001

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24
[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 2: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies in Medication Overuse Subgroup

Efficacy per 28 days	**Pooled Studies 191622-079 & 191622-080**		
	BOTOX® (N=445)	Placebo (saline) (N=459)	p- value
Mean change from baseline in frequency of headache days[a]	-8.2	-6.2	<0.001
Mean change from baseline in frequency of migraine/probable migraine days[a]	-8.1	-6.0	<0.001
Mean change from baseline in number of moderate/severe headache days[a]	-7.7	-5.7	<0.001
Mean change from baseline in total cumulative hours of headache on headache days[a]	-111.91	-73.26	<0.001
Mean change from baseline in frequency of headache episodes[a]	-5.6	-4.9	0.028
Proportion of patients with severe HIT-6[b] category scores	71.0%	81.9%	<0.001
Total HIT-6 scores[b]	-4.7	-2.2	<0.001
Mean change from baseline in MSQ scores[b]			
Role function- Restrictive	-16.9	-7.6	<0.001
Role function- Preventative	-13.9	-5.8	<0.001
Role function- Emotional Function	-18.3	-8.7	<0.001

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24
[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 3: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies in No Medication Overuse Subgroup

Efficacy per 28 days	**Pooled Studies 191622-079 & 191622-080**		
	BOTOX® (N=445)	Placebo (saline) (N=459)	p- value
Mean change from baseline in frequency of headache days[a]	-8.8	-7.3	0.013
Mean change from baseline in frequency of migraine/probable migraine days[a]	-8.4	-6.6	0.004
Mean change from baseline in number of moderate/severe headache days[a]	-7.7	-6.1	0.005
Mean change from baseline in total cumulative hours of headache on headache days[a]	-128.75	-99.73	0.023
Mean change from baseline in frequency of	-5.1	-4.5	0.146

headache episodes[a]			
Proportion of patients with severe HIT-6[b] category scores	61.3%	70.9%	0.027
Total HIT-6 scores[b]	-5.1	-2.7	<0.001
Mean change from baseline in MSQ scores[b]			
Role function- Restrictive	-17.2	-10.6	0.001
Role function- Preventative	-11.7	-7.7	0.032
Role function- Emotional Function	-17.4	-11.0	0.017

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24
[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 4: Week 24 (Primary Timepoint) Key Efficacy Variables for Phase 3 Studies

Efficacy per 28 days	Study 191622-079			Study 191622-080		
	BOTOX® (N=341)	Placebo (saline) (N=338)	p- value	BOTOX® (N=347)	Placebo (saline) (N=358)	p- value
Mean change from baseline in frequency of headache days[a]	-7.8	-6.4	0.006	-9.0	-6.7	<0.001
Mean change from baseline in frequency of migraine/probable migraine days[a]	-7.6	-6.1	0.002	-8.7	-6.3	<0.001
Mean change from baseline in number of moderate/severe headache days[a]	-7.2	-5.8	0.004	-8.3	-5.8	<0.001
Mean change from baseline in total cumulative hours of headache on headache days[a]	-106.70	-70.40	0.003	-132.41	-90.01	<0.001
Mean change from baseline in frequency of headache episodes[a]	-5.2	-5.3	0.344	-5.3	-4.6	0.003
Proportion of patients with severe HIT-6 category scores[b]	68.9%	79.9%	0.001	66.3%	76.5%	0.003
Total HIT-6 scores[b]	-4.7	-2.4	<0.001	-4.9	-2.4	<0.001
Mean change from baseline in MSQ scores[b]						
Role function- Restrictive	-16.8	-8.8	<0.001	-17.2	-8.4	<0.001
Role function- Preventative	-12.6	-7.6	0.005	-13.5	-5.4	<0.001
Role function- Emotional Function	-16.9	-10.0	0.001	-19.0	-9.1	<0.001

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24
[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Blepharospasm

In one study, botulinum toxin was evaluated in 27 patients with essential blepharospasm. Twenty-six of the patients had previously undergone drug treatment utilising 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, twelve 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.

In a separate study, blepharospasm patients received an average dose per eye of 33 U of BOTOX® injected at 3 to 15 sites. The most frequently reported treatment-related adverse events were ptosis (20.8%), superficial punctate keratitis and eye dryness (6.3% each).

Strabismus
Six hundred and seventy-seven adult patients with strabismus treated with one or more injections of BOTOX® were evaluated in a large retrospective case review. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection (1). Large strabismus angles tended to return to pre-injection position and required re-injection more frequently than smaller angles. Thirty-five percent of adults with horizontal strabismus were corrected by one injection to within 10 prism diopters of orthoposition.

Focal spasticity in children 2 years and older

Upper limb spasticity
Two randomised, evaluator-blinded studies compared BOTOX® plus standard care with standard care alone in a total of 72 children with hemiplegic cerebral palsy and upper limb spasticity. In these studies the muscles in the arm and hand that were injected included the biceps brachii, brachialis, brachioradialis, flexor carpi ulnaris and radialis, pronator teres, pronator quadratus, flexor digitorum profundus and sublimis, flexor pollicis longus and brevis, thumb adductor, short flexor of the thumb and interossei.

In the 6-month study (n = 42; 2 to 8 years) spasticity as measured by the Modified Ashworth Scale (MAS) was significantly reduced in children treated with BOTOX® (1-2 U/kg/muscle, maximum dose 240 units, mean 137 units) at months 1 and 3, but returned to baseline values at month 6. Quality of upper limb movement as measured by the Quality of Upper Extremity Skills Test (QUEST) improved significantly from baseline in both groups but to a greater extent in BOTOX®–treated children at months 1 (61% vs. 19%, p=0.004) and 3 (71% vs 33%, p=0.03), but not at month 6 (p=1.0). Children treated with BOTOX® had a significantly greater improvement in function as measured by Goal Attainment Scaling (GAS). Children treated with BOTOX® improved more quickly than those treated with standard care alone. No treatment-related adverse effects were reported.

In the three month study (n = 30, 5-15 years) upper limb function was measured using the Melbourne Assessment of Unilateral Upper Limb Function. Children in the BOTOX® group

(0.5 to 2.0 U/kg/muscle) had a 14% improvement in function compared with no change in children in the control group at month 3 (p = 0.002). In this study, there was no difference between treatment groups on the GAS. Three treatment-related adverse effects were reported, 2 localised weakness and one increased frequency of micturition.

Lower limb spasticity – Equinus
A three-month, double-blind, placebo-controlled parallel study was conducted in , cerebral palsy children, aged 2 to 16 years with equinus ankle position. Seventy-two were administered 4U/kg body weight of BOTOX® into the medial and lateral heads of the gastrocnemius at baseline (2 U/kg/muscle), for hemiplegic patients and 1 U/kg/muscle for diplegic patients) and again at 4 weeks. The cumulative dose of BOTOX® over 4 weeks was 2-4 U/kg/muscle and overall 8 U/kg body weight up to a maximum of 200 units during a 30 day period. BOTOX® was significantly more effective than placebo (as assessed by improvement of 3 or more grades on the composite score of Rating Scale (PRS) of dynamic gait (gait pattern, ankle position, hindfoot position during foot strike, knee position during gait, degree of crouch and speed of gait). Improvement was reported by 53%, 50%, 60% and 54% of BOTOX® patients versus 25%, 27%, 25% and 32% of placebo patients at weeks 2, 4, 8 and 12, respectively. Of the individual assessments included on the PRS, a significantly greater number of BOTOX® patients versus placebo patients had improvements in gait pattern (weeks 2, 8 and 12) and ankle position (weeks 2, 6 and 12).

In the 39 month long-term, open-label follow-up of these patients, the medial and lateral gastrocnemius muscles were injected at a dose of 2 U/kg/muscle with a maximum total dose of 200 U of BOTOX® into the medial and lateral heads of the gastrocnemius, and then as needed thereafter. Of the 207 patients evaluated; 115 patients were followed for 12 months, 100 for 18 months, 45 for 2 years and 6 for up to 3 years. The percent of patients who showed an improvement based on the PRS ranged from 41% to 67% over the 3-year period. Of the individual assessments which were included in the PRS, significant improvements were seen at every visit over the 3-year period.

Lower limb spasticity – hip adductor
Published studies showed that BOTOX® is effective in reducing pain and spasticity and improving function. A double-blind placebo-controlled study[8] (n=16) in children aged 2 to 10 years found that 4U/kg body weight to each adductor muscle group (total dose 8 units/kg total body weight) administered 5 -10 days before scheduled isolated adductor surgery significantly reduced mean pain scores (74% reduction, p=0.003), analgesic requirements (50% reduction, p=0.005) and length of hospital stay (33% reduction, p=0.003) compared with placebo.

A second study[9] (n = 43, mean age 8.2 ± 2.5 years) compared the efficacy of BOTOX® (300 U injected into the adductor and medial hamstring muscles) with a pressure splint against hip adductor muscle spasticity. Both groups improved during the study period, however, at the 3 month visit, BOTOX® was significantly more effective than pressure splints for spasticity and motor performance as measured by the MAS (p=0.002) and knee distance (p=0.02).

Adverse events were not reported in these studies.

Focal spasticity in adults
Three double-blind placebo-controlled studies involving 256 post-stroke patients with upper

limb spasticity showed clinically and statistically significant improvements in wrist, elbow and finger flexor muscle tone. The Ashworth scale was used to measure clinically significant changes in muscle tone which was assessed from a score of zero (no increase in muscle tone) to 4 (limb rigid in flexion or extension).

In one study, 126 patients were treated with 200 U to 240 U of BOTOX® into the wrist, finger and thumb flexor muscles. A clinically and statistically significantly greater reduction in muscle tone was observed in BOTOX®-treated patients compared to placebo as measured on the Ashworth scale ($p<0.001$) at 1, 4, 6, 8, and 12 weeks post-treatment. The Physician Global Assessment also showed statistically significant improvements at all post-treatment visits for these patients ($p < 0.001$). Furthermore, patients treated with BOTOX® had significant improvement for a pre-determined, targeted disability item associated with upper limb spasticity at 4, 6, 8 and 12 weeks post-treatment (p£0.05).

In two studies, patients treated with a total dose of either 300 U or 360 U of BOTOXÒ had significantly greater reduction in wrist and elbow flexor tone compared to placebo. Additionally, the Physician Global Assessment also showed significant benefit from BOTOXÒ at doses of 75, 180 and 360 U.

In a double-blind, placebo-controlled study of 85 patients with moderate to severe lower limb spasticity, injections of up to 300 U of BOTOXÒ into the soleus, posterior tibialis and either gastrocnemius or flexor digitorum longus muscles resulted in a reduction of spasm frequency, a reduction in pain, an improvement in spasticity as rated by the physician and increase in range of motion of the ankle as measured by goniometry. All of these changes were clinically and statistically significant. In addition, treatment with BOTOXÒ in patients with severe spasticity (Ashworth score of 3) resulted in a clinically and statistically significant reduction in muscle tone. In an open-label follow-up to this study, a second injection of BOTOXÒ clinically and statistically significantly reduced muscle tone in both moderate and severe patients at 4, 8 and 12 weeks post 2nd injection.

Cervical Dystonia (spasmodic torticollis)

In a multicentre study, 170 cervical dystonia patients who had responded to an open-label run-in period (out of 214 patients) were randomised to receive BOTOXÒ (n=88) or placebo (n=82) in a double-blind, parallel-group evaluation for 10 weeks. Physicians determined the muscles and doses injected for each patient and used a mean total body BOTOXÒ dose of 236 U (Range: 95 to 360 U). BOTOXÒ was significantly better compared with placebo by measures of improvement in the Cervical Dystonia Severity Scale (head position rating), physician global assessment, patient global assessment, frequency and intensity of pain, and functional disability by week 6, with sustained benefit for up to 10 weeks. Improvement, as measured by physician global assessment, was 50.6% for the BOTOXÒ group and 31.1% for the placebo group, a difference of 19.5% ($p=0.009$), which was essentially the same as the pre-defined value of 20% set for a clinically meaningful difference.

In a separate multicentre study, a total of 135 patients were treated. Patients received a single 100-300 U injection of one formulation followed by the other, 8-16 weeks later. Physicians determined the muscles and doses to be injected for each patient and used a mean total body BOTOX® dose of approximately 155 U for all treatment periods. Maximum clinical improvement was observed at 6 weeks, with over 80% of patients achieving a treatment

success by week 6. In relation to time-to-retreatment, at week 6 (42 days) post-injection, 67% of the BOTOX® group had not yet worsened since baseline compared to 45% of the placebo group. At week 10 (70 days) post-injection, 60% of the BOTOX® group remained improved compared to 30% in the placebo group. These differences were statistically significant (p=0.0002).

Primary Hyperhidrosis of the Axillae

In a double-blind, parallel-group, multicentre study, 320 patients with bilateral axillary primary hyperhidrosis were randomised to receive BOTOX® (n=242) or placebo (n=78). Subjects were eligible for enrolment in the study if their baseline spontaneous axillary, as measured by gravimetric assessment over 5 minutes at room temperature and at rest, was $\geq$ 50 mg. Baseline axillary sweat production was similar in the two treatment groups (216 mg in the BOTOX® group and 236 mg in the placebo group). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric assessment.

The incidence of responders among BOTOX®-treated patients was significantly higher ($p<0.001$) than placebo-treated patients at all post-treatment time points for up to 16 weeks. The incidence of responders among BOTOX®-treated patients ranged from 95% at week 1 to 82% at week 16 compared to 32% at week 1 to 21% at week 16 for placebo-treated patients. The mean percentage reduction in the BOTOX®-treated group ranged from 83% at week 1 to 69% at week 16 compared to 22% at week 1 to 4% at week 16 in the placebo-treated group. The corresponding mean amounts of sweat production at these timepoints were 29 mg and 54 mg in the BOTOX®-treated patients compared to 166 mg and 190 mg in the placebo-treated patients.

Subject's global assessment of treatment satisfaction was significantly higher ($p<0.001$) in BOTOX®-treated than placebo-treated patients at all post-treatment timepoints.

Spasmodic Dysphonia

In the largest series reported 639 patients with adductor spasmodic dysphonia and 108 patients with abductor spasmodic dysphonia were injected with a mean dose of 3.1 ± 3.1 units and 2.16 ± 1.07 units of BOTOX® respectively. The patients recorded the responses in a diary, including their percentage of normal function, on a global visual analogue scale where 100% was a normal voice and 0% was inability to phonate. For adductor spasmodic dysphonia the mean onset of effect was 2.4 ± 4.3 days with a mean peak effect of 9 ± 12.7 days. The mean duration of benefit was 15.1 ± 12.3 weeks, the percent of normal function rose from 52.4% ± 22% to 89.71% ± 13%. For abductor spasmodic dysphonia mean onset of effect was 4.1 ± 5.5 days with a mean peak effect of 10 ± 12.5 days. The mean duration of benefit was 10.5 ± 12.2 weeks. The percentage of normal function rose from 54.8% ± 21.9% to 66.7% ± 23.4% respectively.

In another large series of 169 patients (adductor spasmodic dysphonia 88.8%, abductor spasmodic dysphonia 1.8% and mixed spasmodic dysphonia 4.1%) the median treatment outcome score was excellent in 63.9% of patients, very good in 18%, satisfactory in 14.5% and unsatisfactory in 3.5%, as judged by a subjective self-rating scale which patients recorded in a diary. Speech rate increased after BOTOX® therapy by approximately 12 syllables per minute. Nasendoscopy, before and after treatment in many patients, confirmed the weakening of the vocal cords and abolition of the spasms.

CLINICAL TRIALS – Cosmetic Indications

Glabellar Lines

In two multicentre, double-blind, placebo-controlled, parallel-group studies of identical design, patients with moderate to severe glabellar lines evaluated at maximum frown were randomised to receive BOTOX^{Ò} (n=405) or placebo (n=132). In these studies, the severity of glabellar lines was significantly reduced for up to 120 days in the BOTOX^{Ò} group compared to the placebo group as measured by investigator rating of glabellar line severity at maximum frown and at rest, and by subjects global assessment of change in appearance of glabellar lines. Thirty days after injection, 80% of BOTOX^{Ò}-treated patients were considered by investigators as treatment responders (glabellar line severity score of mild or none), and 89% of patients felt they had moderate or better improvement, compared to 3.0% and 6.8% of placebo-treated patients respectively.

A third, open-label study was also conducted to support the continued efficacy of repeat BOTOX^{Ò} injections. At the completion of the double-blind studies, patients were able to enter this open-label phase with repeat treatments given at 120 day intervals. Therapeutic effect was maintained over the three injection cycles assessed with results showing increased efficacy following multiple injection sessions.

Crow's Feet

Two multicentre, double-blind, placebo-controlled, parallel-group studies were performed to examine the safety and efficacy of BOTOX® for the treatment of crow's feet. In one study, patients with bilaterally symmetrical, moderate or severe crow's feet at maximum smile were randomised to receive BOTOX® (n=130) [age range 27 to 64 years (mean = 47 years)], injected bilaterally at three sites per side, for a dose of 3 U, 6 U, 12 U or 18 U per side or placebo (n=32). Treatment with BOTOX® showed a dose-related response up to 12 U; although the response was similar in the two highest dose groups, 12 U and 18 U. The duration of response was dose-related, with significant mean reductions from baseline in crow's feet severity to day 180 for the 12 U ($p \leq 0.032$) and 18 U ($p \leq 0.003$) groups, day 150 for the 6 U group ($p \leq 0.017$) and day 120 for the 3 U group ($p \leq 0.006$). No significant changes were seen within the placebo group at any post-treatment timepoint. Maximum responder rates were observed at day 30 for all treatment groups. The safety profile in the active treatment groups was similar to placebo.

The second study examined the safety and efficacy of treatment of crow's feet with 1 of 3 dosages of BOTOX® (n=148) or placebo (n=49) [age range 27 to 65 years (mean = 47 years)], and the effect on the severity of forehead lines and glabellar lines. In this study, patients with bilaterally symmetrical, moderate or severe crow's feet at maximum smile; forehead line severity of mild, moderate or severe at maximum eyebrow elevation and glabellar line severity of mild, moderate or severe at maximum frown were treated with BOTOX®, injected bilaterally at three sites per side, for a dose of 6 U, 12 U or 18 U per side or placebo. Although significant improvements in crow's feet were seen with all BOTOX® doses when compared to placebo, the treatment of crow's feet did not affect the severity of either horizontal forehead lines or glabellar lines. Thus it appears that the treatment of crow's feet at doses of 18 U, 12 U and 6 U does not affect adjacent areas and as such dose modification is not considered necessary. No safety concerns were seen at any dose of BOTOX® treatment.

The safety and efficacy of BOTOX® for the treatment of crow's feet has been described in published clinical studies. In one study, 60 patients were treated with 6 U, 12 U or 18 U of BOTOX® in the orbicularis oculi muscle on one side of the face and placebo contralaterally. At 16 weeks after injection, patients were treated with 12 U or 18 U of BOTOX® bilaterally. BOTOX® was associated with significantly higher success rates than placebo at all dose levels, as determined by both trained observers and patients. At 4 weeks post-injection, 89-95% of patients on the BOTOX®-treated side were considered by investigators as treatment responders and 60-80% of patients felt they had treatment success, compared to approximately 5-15% and 15-45%, respectively on the placebo treated side. No clear dose response relationship was observed. Benefits of the second injection lasted longer than the first, with success rates for the second injection reaching 100% for the 12 U and 18 U groups at week 4. BOTOX® was well tolerated. No serious or severe adverse events were reported.

Forehead Lines

The safety and efficacy of BOTOX® for the treatment of horizontal forehead lines has been described in published clinical studies. In one study, BOTOX® was administered to 59 patients with horizontal forehead lines scoring 2 (moderate) or 3 (severe) on the facial wrinkle scale (FWS). Patients were randomly assigned to receive 8 U, 16 U and 24 U of BOTOX® injected into the frontalis muscle with additional brow depressor injections. Approximately 90% of subjects responded to treatment as rated by investigators and up to 75-80% by self-assessment at week four. There was a reduction in horizontal rhytide severity in all three BOTOX® treatment groups at both contraction and repose. There was a significant dose-response trend ($p \leq 0.019$) for sustained duration of improvement: 53% in the 24 U group versus 15% in the 8 U group at 16 weeks ($p \leq 0.023$ for difference between groups), by trained observer. There was a significant dose-response trend ($p \leq 0.011$) for rate of relapse to baseline: 35% in the 24 U group versus 75% in the 8 U group at 16 weeks ($p \leq 0.038$ for difference between groups), by trained observer. BOTOX® was well tolerated. No serious adverse events were reported.

INDICATIONS

BOTOXÒ (botulinum toxin type A) purified neurotoxin complex is indicated for the following therapeutic indications:

- treatment of overactive bladder with symptoms of urinary incontinence, urgency and frequency, in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication
- treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents
- prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
- treatment of strabismus in children and adults
- treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth nerve disorders (specifically hemifacial spasm) in patients twelve years and over
- treatment of cervical dystonia (spasmodic torticollis)
- treatment of focal spasticity of the upper and lower limbs, including dynamic equinus

foot deformity, due to juvenile cerebral palsy in patients two years and older
- treatment of severe primary hyperhidrosis of the axillae
- treatment of focal spasticity in adults
- treatment of spasmodic dysphonia.

BOTOX^{Ò} (botulinum toxin type A) purified neurotoxin complex is indicated for the following cosmetic indications:
- temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.

CONTRAINDICATIONS

BOTOX^{Ò} (botulinum toxin type A) purified neurotoxin complex is contraindicated in individuals with known hypersensitivity to any ingredient in the formulation.

BOTOX^{Ò} is contraindicated in patients with myasthenia gravis or Eaton Lambert Syndrome.

BOTOX^{Ò} is contraindicated in the presence of infection at the proposed injection site(s).

Bladder Dysfunction

Intradetrusor injection of BOTOX® is contraindicated in patients who have acute urinary tract infection, and in patients with acute urinary retention who are not routinely catheterising.

Due to the risk of urinary retention, intradetrusor injection of BOTOX® is also contraindicated in patients who are not willing and/or able to initiate catheterisation post-treatment, if required (See **Clinical Trials**).

PRECAUTIONS
General

Lack of interchangeability between botulinum toxin products
DUE TO THE LACK OF AN INTERNATIONAL UNIT, BOTOX^{Ò} IS NOT THERAPEUTICALLY EQUIVALENT TO ANY OTHER BOTULINUM TOXIN TYPE A PREPARATIONS. THE POTENCIES OF BOTOX^{Ò} AND OTHER BOTULINUM TOXIN TYPE A PREPARATIONS ARE BASED ON DIFFERENT ASSAY METHODS. IN VIEW OF THIS LACK OF HARMONISATION OF UNIT SYSTEMS FOR BOTULINUM TOXIN TYPE A, EXTREME CAUTION IS REQUIRED IF IT SHOULD PROVE NECESSARY TO SUBSTITUTE THE BOTULINUM TYPE A TOXIN OF ONE PHARMACEUTICAL COMPANY BY ANOTHER. 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.

Spread of toxin effect

Postmarketing 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 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 these symptoms can also occur in patients who have underlying conditions and co-morbidities 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 there have been reports of death, although an exact relationship to BOTOX® has not been established. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur.

Pre-existing neuromuscular disorders
Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) should only receive BOTOX^{Ò} with extreme caution. Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX^{Ò}. Published medical literature has reported rare cases of administration of botulinum toxin to patients with known or unrecognised neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. When exposed to very high doses, patients with neurologic disorders, e.g. paediatric cerebral palsy or adult spasticity may also be at increased risk of clinically significant systemic effects.

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 oedema, and dyspnoea. 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.

The recommended dosages and frequencies of administration for BOTOX^{Ò} should not be exceeded (see **Dosage and Administration**).

Formation of neutralising 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 neutralising antibody formation have not been well characterised. The potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections.

There have been rare reports of adverse events following administration of BOTOX®

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. The exact relationship of these events to BOTOX® has not been definitely established and will continue to be monitored by Allergan Australia Pty Ltd.

The safe and effective use of BOTOXÒ (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 BOTOXÒ should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. Care should be taken when injecting near vulnerable anatomic structures and direct injection into these structures must be avoided.
Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax **,** and therefore extreme caution is required when injecting in this area. Caution is warranted when injecting in proximity to the lung, particularly the apices. An understanding of standard electromyographical techniques may be useful for the treatment of hemifacial spasm, cervical dystonia (spasmodic torticollis) and for the treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients.

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

As with any injection, procedure-related injury could occur. An injection could result in localised infection and pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

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.

This product contains human serum 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.

Bladder Dysfunction

The intradetrusor administration of BOTOX® is only to be conducted by a urologist/urogynaecologist who has been trained in this highly specialised technique or by a urologist/urogynaecologist under the direct supervision of a urologist/urogynaecologist who has been so trained.

Appropriate medical caution should be exercised when performing a cystoscopy.

In patients who are not catheterising, BOTOX® may decrease their ability to fully empty the bladder due to the pharmacological mode of action on the detrusor contractions. Therefore, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks in these patients. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required. Patients who develop an increase in post-void residual urine and/ or patients who start to catheterise may have an increased risk of developing urinary tract infections. Patients who are not catheterising need to be made aware of this prior to treatment.

Patients who are not catheterising and who subsequently develop a clinically relevant increase in post-void residual urine, may need to start to catheterise to achieve desired efficacy (See **Clinical Trials**).

Overactive Bladder

Urinary Retention
In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterisation (CIC) for urinary retention following treatment with BOTOX® or placebo is shown in the Table below. The duration of post-injection catheterisation for those who developed urinary retention is also shown.

Proportion of Patients Catheterising for Urinary Retention and Duration of Catheterisation following an injection in double-blind, placebo-controlled clinical trials in OAB

Timepoint	**BOTOX® 100 Units (N=552)**	**Placebo (N=542)**
Proportion of Patients Catheterising for Urinary Retention		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
Duration of Catheterisation for Urinary Retention (Days)		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX® were more likely to develop urinary retention than those without diabetes, as shown in the Table below.

Proportion of Patients Experiencing Urinary Retention following an injection in double-blind, placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus

	Patients with Diabetes		**Patients without Diabetes**	
	BOTOX® 100 Units (N=81)	Placebo (N=69)	BOTOX® 100 Units (N=526)	Placebo (N=516)

Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Urinary Tract Infection
BOTOX® increases the incidence of urinary tract infection (see Adverse Effects). Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX® for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

Use in Males
The pivotal studies in overactive bladder were not powered for a subgroup analysis based on gender, however a statistically significant treatment-by-gender interaction was demonstrated. No statistically significant benefit was demonstrated in males for incontinence frequency or on the Treatment Benefit Scale (see Clinical Trials). In men, 12.2% of the overall study population, mean incontinence was decreased by 0.42 episodes per day (by LS mean difference) relative to placebo (p=0.612) from a baseline of 5.6 episodes per day, whereas in women it was reduced by 2.0 episodes (p<0.001). The proportion of men who felt that treatment had led to improvement on the Treatment Benefit Scale was ~40% (p=0.060), with the attributable proportion being 15% (after subtracting the placebo response of 25%). Approximately 60% of men given BOTOX® for overactive bladder felt that their condition was unchanged or worsened after treatment. Men considering BOTOX® for overactive bladder should be made aware of the gender specific results, including potential risk of urinary tract infections (BOTOX® 9.5% vs placebo 2.6%) and urinary retention (BOTOX® 7.9% vs placebo 1.3%).

Men with overactive bladder and signs or symptoms of urinary obstruction should not be treated with BOTOX®.

Please refer to the **Adverse Events-General section** for local weakness or weakness of adjacent muscles.

Neurogenic Detrusor Overactivity
In these patients, autonomic dysreflexia associated with the procedure could occur, which may require prompt medical therapy.

Safety and efficacy data beyond two intradetrusor treatments are limited.

Blepharospasm
Reduced blinking following BOTOX® injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with cranial nerve VII 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 medial 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.

As a result 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. Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin.

Strabismus
BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX® treatment in deviations over 50 prism dioptres, 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. In order to enhance efficacy, multiple injections over time may be required.

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

Spasticity
BOTOX^{Ò} is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens and is not intended as a replacement for these treatment modalities. BOTOX^{Ò} treatment is not likely to be effective in improving range of motion at a joint affected by a known fixed contracture.
Identification of treatment goals and clinical examination to identify the specific muscles causing spasticity is necessary, and use of electromyography, muscle ultrasound or electrical stimulation may facilitate the accuracy of the BOTOX^{Ò} injections.
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. Caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

Cervical Dystonia (spasmodic torticollis)
Dysphagia and Breathing Difficulties
Treatment with BOTOX^{Ò} and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting 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 swallowing. When distant effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Primary Hyperhidrosis of the Axillae
Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Spasmodic Dysphonia
The diagnosis of spasmodic dysphonia should also be established by a multidisciplinary approach including neurological, ENT and speech pathology assessment. Laryngoscopy (preferably by a nasendoscope) is mandatory during the diagnostic evaluation to exclude other structural disorders of the larynx causing any form of dysphonia and to observe the nature of the hyperadductive or hyperabductive movements.

In general, treatment of spasmodic dysphonia with BOTOX® injections should not be administered in pregnant or breastfeeding women. It should be avoided in patients who are due to have elective surgery requiring general anaesthetic as BOTOX® relaxes the vocal cords, potentially increasing the risk of peri-operative aspiration etc. It is recommended that this procedure be carried out by appropriately trained physicians in facilities prepared to manage reflex stridor should it occur in association with the procedure.

Upper Facial Rhytides (forehead lines, crow's feet and glabellar lines)
Reduced blinking from BOTOX® injection of the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve VII disorders. Caution should be used when BOTOX® treatment is used in patients who have an inflammation 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.

Chronic migraine
Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with BOTOX^{Ò} should be evaluated by a neurologist or pain management specialist prior to receiving treatment with BOTOX^{Ò}. The use of BOTOX^{Ò} for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles over 32 weeks. No long term safety or efficacy data for this indication

are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

The safety and effectiveness of BOTOX® have not been established for the prophylaxis of headaches in adults with episodic migraine (14 headache days or fewer per month) or tension type headache.

Carcinogenicity
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX® injection. BOTOX® is not structurally related to any known carcinogens.

Genotoxicity
BOTOX® was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity.

Effects on Fertility
Intramuscular BOTOX® doses of 4 U/kg (males) and 8 U/kg (females) did not affect rat fertility. Decreased fertility occurred with higher doses, which also resulted in signs of toxicity. The relevance of these findings to human fertility is not known.

Use in Pregnancy: Pregnancy Category B3.
There are no adequate data regarding the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. BOTOX® should not be used during pregnancy unless the benefits clearly outweigh the potential risks. If the use of BOTOX® is determined to be warranted during pregnancy, or if the patient becomes pregnant whilst being treated with BOTOX®, the patient should be apprised of the potential risks.

There was no evidence of teratogenicity in animal studies. Intramuscular administration of BOTOX® to mice and rats during the period of organogenesis reduced dam weight gain and fetal ossification (4 U/kg); higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification. Intramuscular administration to rabbits twice during the period of organogenesis resulted in abortions (2 U/kg) and maternal deaths (4 and 6 U/kg), while daily intramuscular administration during organogenesis resulted in reduced fetal weights (0.25 and 0.5 U/kg) and increased resorptions (0.5 U/kg); the no-effect dose was 0.125 U/kg, although all doses were maternotoxic. Intramuscular treatment of rats with a maternotoxic dose of BOTOX® (16 U/kg) twice during gestation and once during lactation resulted in increased post-implantation loss and reduced pup weights, but post-weaning pup development was unaffected. The significance of the adverse findings in animals for clinical risk is uncertain.

Use in Lactation
There is no information on whether BOTOX® is excreted in human milk. The use of BOTOX® during lactation is not recommended.

Paediatric Use
The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to

overactive bladder have not been established in patients below the age of 18 years.

The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to neurogenic detrusor overactivity have not been established in patients below the age of 18 years.

Safety and effectiveness in paediatric patients below the age of 18 years have not been established for the indication of chronic migraine.

Safety and effectiveness in children below the age of 12 years have not been established for the indications of blepharospasm, hemifacial spasm, cervical dystonia, hyperhidrosis, spasmodic dysphonia or upper facial lines (forehead, crow's feet and glabellar lines). The safety and effectiveness of BOTOX® in the treatment of focal spasticity has not been investigated in children under two years of age.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. A causal association to BOTOX® has not been established in these cases and will continue to be monitored by Allergan Australia Pty Ltd. Some of these patients had risk factors including significant neuromuscular debility, dysphagia, aspiration pneumonia, seizures and cardiovascular disease. Post-marketing reports of possible distant effects from the site of injection have been very rarely reported in paediatric patients with co-morbidities, predominately with cerebral palsy who received >8 U/kg. Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

New onset or recurrent seizures have also been reported, typically in children who are predisposed to experiencing these events. The exact relationship of these events to the BOTOXÒ injection has not been established.

Use in the Elderly
The reported clinical experience has not identified 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.

Overactive Bladder
Of 1242 patients in placebo-controlled clinical studies of BOTOX®, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=l82) were 75 years of age or older. No overall difference in the safety profile following BOTOX® treatment was observed between patients aged 65 years and older compared to younger patients in these studies, with the exception of urinary tract infection. In the placebo group, the incidence of urinary tract infection was higher in patients 65 years of age or older compared to younger patients (15.2% vs. 6.6%, respectively). The incidence was also higher in patients 65 years and older who were given BOTOX® compared to younger patients (33.1% vs. 21.2 %, respectively). No overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical studies.

Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in

Patients with OAB

	<65 Years		65 to 74 Years		≥75 Years	
Adverse Reactions	BOTOX® 100 Units (N=344)	Placebo (N=348)	BOTOX® 100 Units (N=169)	Placebo (N=151)	BOTOX® 100 Units (N=94)	Placebo (N=86)
Urinary tract infection	73 (21%)	23 (7%)	51 (30%)	20 (13%)	36 (38%)	16 (19%)
Urinary retention	21 (6%)	2 (0.6%)	14 (8%)	0 (0%)	8 (9%)	1 (1%)

Effects on the ability to drive and use machines
Asthenia**,** muscle weakness**,** dizziness and visual disturbance have been reported after treatment of BOTOX® and could make driving or using machines dangerous.

Interactions with other Medicines
The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or any other drugs that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants). Caution should be exercised when BOTOXÒ is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmycin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs which interfere with neuromuscular transmission.

No specific tests have been carried out to establish the possibility of clinical interaction with medicinal products. No drug interactions of clinical significance have been reported.

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

Information for Patients

Patients should be informed that the BOTOX® Consumer Medicines Information leaflet is available and must be provided to them by prescribers.

If BOTOXÒ is used during pregnancy, or if the patient becomes pregnant while being treated with BOTOXÒ, the patient should be apprised of the potential risks, including abortion seen in animal studies.

Patients with cervical dystonia (spasmodic torticollis) should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Consequent to the dysphagia there is the potential for aspiration and/or dyspnoea. In rare cases, tube feeding, aspiration pneumonia and death have been reported. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Patients or caregivers should be advised to seek immediate medical consultation if swallowing, speech or respiratory disorders arise.

After bladder injections for urinary incontinence, patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required.Patients

not already catheterising prior to BOTOX® bladder injections, should be advised to attend a clinic visit approximately 2 weeks after the procedure for measurement of their post-void residual volume.

Patients who are not catheterising and who subsequently develop a clinically relevant increase in post-void residual urine, may need to start to catheterise to achieve desired efficacy (See **Clinical Trials**).

Effects on Laboratory Tests
There were no significant differences in routine laboratory variables between the placebo and BOTOX® groups in patients receiving doses up to 360 U, for the treatment of cervical dystonia.

ADVERSE EFFECTS

General
In general, adverse events occur within the first few days following injection of BOTOX® and while generally transient may have duration of several months or, in rare cases, longer.
As is expected for any injection procedure, localised pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Local weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles and/or muscles remote from the site of injection has been reported.

Overactive Bladder
Table 5 presents the most frequently reported adverse reactions in double-blind, placebo-controlled, pivotal Phase 3 studies within 12 weeks of injection for overactive bladder.

Table 5: Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks, in Double-blind, Placebo-controlled, Pivotal Phase 3 Clinical Trials

Adverse Reactions by System Organ Class	BOTOX® 100 Unit (N=552)	Placebo (N=542)
Infections and infestations		
Urinary tract infection	17.9%	5.5%
Bacteriuria	4.3%	2.0%
Renal and urinary disorders		6.6%
Dysuria	9.1%	0.4%

Urinary retention Residual urine volume*	5.6% 3.1%	0.2%

*Elevated PVR not requiring catheterisation

During the complete treatment cycle, the following adverse reactions with BOTOX® 100 Units were reported: urinary tract infections (25.5%), dysuria (10.9%), bacteriuria (8.0%), urinary retention (5.8%), residual urine volume (3.4%), and pollakiuria (2.0%).

The following table presents the BOTOX® treated patients and placebo treated patients who initiated CIC at week 12 and anytime during treatment cycle 1.

Catheterisation Rates at Week 12 and Anytime During Treatment Cycle 1

	100 U BOTOX®	**Placebo**
At Week 12	4.0% (22/547)	0.0% (0/535)
Anytime during Treatment cycle 1	6.5% (36/552)	0.4% (2/542)

Urinary tract infections were increased in patients who initiated CIC and those who had post void residual volumes ≥200mL. The following table presents a summary of UTI rates by CIC status and post-void residual urine volume during the first 12 weeks.

Urinary Tract Infection Rates by CIC Status and Post-void Residual Urine Volume During the First 12 Weeks of Treatment Cycle 1

	100 U BOTOX®	**Placebo**
Initiated CIC	39.6% (19/48)	12.5% (1/8)
Did not initiate CIC	15.9% (80/504)	5.4% (29/534)
PVR urine ≥ 200 mL	34.5% (20/58)	0.0% (0/4)
PVR urine < 200 mL	16.0% (79/494)	5.6% (30/538)

CIC = clean intermittent catheterisation; PVR = post-void residual

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX® 100 Units and placebo than in patients without diabetes, as shown in the Table below.

Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus

	Patients with Diabetes		**Patients without Diabetes**	
	BOTOX® 100 Units (N=81)	**Placebo (N=69)**	**BOTOX® 100 Units (N=526)**	**Placebo (N=516)**
Urinary tract infection (UTI)	25 (31%)	8 (12%)	135 (26%)	51 (10%)

Events considered to be procedure-related by the investigator reported at any time following initial injection were dysuria (5.8%) and haematuria (2.2%).

Based on an ongoing open-label extension study, no change was observed in the overall safety profile with repeat dosing.

Neutrogenic Detrusor Overactivity
Table 6 presents the most frequently reported adverse reactions in double-blind studies within 12 weeks of injection for neurogenic detrusor overactivity.

Table 6: Adverse Reactions Reported by ≥1% of BOTOX®-treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks, in Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX® 200 Unit (N=262)	Placebo (N=272)
Infections and infestations Urinary tract infection	24.4%	17.3%
Renal and urinary disorders Urinary retention	17.2%	2.9%
General disorders and administration site conditions Fatigue	3.8%	1.1%
Psychiatric disorders Insomnia	1.5%	0%

The following rates with BOTOX® 200 Units were reported during the complete treatment cycle (median duration of 44 weeks of exposure): urinary tract infections (49.2%), urinary retention (17.2%), fatigue (6.1%), and insomnia (3.1%).

In these neurogenic patients, the following additional adverse reactions were reported during the complete treatment cycle: constipation (4.2%), muscular weakness (3.8%), fall (3.1%), gait disturbance (2.7%), muscle spasm (2.3%), and bladder diverticulum (1.1%).
Procedure-related events in the 200 Unit BOTOX® group included: haematuria (3.8%), dysuria (2.3%), and autonomic dysreflexia (1.5%).
No change was observed in the overall safety profile with repeat dosing.

In the multiple sclerosis (MS) patients enrolled in the pooled pivotal studies, the annualised MS exacerbation rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX® and 0.20 for placebo. The annualised MS exacerbation rates reported in the individual studies, showed differing trends between the two pivotal studies: 0.14 for BOTOX® and 0.22 for placebo for study 191622-515, and 0.36 for BOTOX® and 0.19 for placebo for study 191622-516.

Among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 38.9% following treatment with BOTOX® 200 U versus 17.3% on placebo.

In the pivotal studies of neurogenic detrusor overactivity, in the subgroup not using catheterisation at baseline, only 10.1 % of placebo recipients had commenced catheterisation at Week 12, compared to 25.5% of the 200 U group. Urinary tract infections were increased in patients who developed elevated residual volumes, even if they did not commence catheterisation.

The following table presents a summary of UTI rates by pre- and post-treatment CIC status and post-void residual urine volume during the first 12 weeks.

Summary of UTI Rates by Pre- and Post-treatment CIC Status and post-void Residual Urine Volume During the First 12 Weeks

CIC Status		200U BOTOX®	Placebo
Pre-treatment	**Post-treatment**		
Using CIC	**Using CIC**[a]	22.0% (29/132)	20.7% (29/140)
Not Using CIC	**Using CIC**	40.4% (19/47)	11.9% (5/42)
	Not Using CIC	21.3% (13/61)	16.4% (10/61)
	Not Using CIC and PVR urine ≥ 200 mL	32.0% (8/25)	0.0% (0/5)
	Not Using CIC and PVR urine < 200 mL	13.9% (5/36)	17.9% (10/56)

CIC = clean intermittent catheterisation; PVR = post-void residual

[a] Patients who were using CIC pre-treatment continued to use it post-treatment

Chronic Migraine

Safety data were compiled from two Chronic Migraine double-blind, placebo-controlled studies involving 687 patients treated with BOTOX®. The following adverse reactions were reported.

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

Adverse Reactions	BOTOX® N=687	Placebo N=692
Nervous system disorders		
Headache	32 (4.7%)	22 (3.2%)
Migraine	26 (3.8%)	18 (2.6%)
Facial paresis	15 (2.2%)	0 (0.0%)
Eye disorders		
Eyelid ptosis	25 (3.6%)	2 (0.3%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (8.7%)	19 (2.7%)
Musculoskeletal stiffness	25 (3.6%)	6 (0.9%)
Muscular weakness	24 (3.5%)	2 (0.3%)
Myalgia	21 (3.1%)	6 (0.9%)
Musculoskeletal pain	18 (2.6%)	10 (1.4%)
Muscle spasms	13 (1.9%)	6 (0.9%)
Muscle tightness	9 (1.3%)	3 (0.4%)
General disorders and administration site conditions		
Injection site pain	23 (3.3%)	14 (2.0%)
Skin and subcutaneous tissue disorders		
Pruritus	7 (1.0%)	2 (0.3%)
Rash	7 (1.0%)	6 (0.9%)

Migraine, including worsening migraine, was reported in 3.8% of BOTOX® and 2.6% of placebo (saline) patients, typically occurring within the first month after treatment. These reactions did not consistently reoccur with subsequent treatment cycles, and the overall incidence decreased with repeated treatments.

Other adverse reactions reported more frequently in the BOTOX® group compared to the placebo group at a frequency less than 1% include: dysphagia, pain in jaw, and pain of skin.

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX® vs. 1.2% for placebo (saline).

Blepharospasm

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

Ptosis	11.0%
Irritation/tearing (includes dry eye, lagophthalmos and photophobia)	10.0%
Ectropion, keratitis, diplopia and entropion were reported rarely	<1.0%

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

Diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection were reported infrequently in clinical studies.

In two cases of VIIth nerve disorder (one case of an aphakic eye) reduced blinking from BOTOX^{Ò} injection of the orbicularis muscle 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^{Ò} therapy. Sedentary patients should be cautioned to resume activity slowly and carefully following the administration of BOTOX^{Ò}.

Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin (See **Precautions**).

Strabismus
In a clinical investigation of botulinum toxin use in strabismus over a 9-year period, the incidence rates (% injections) of adverse events from 8,300 injections are reported (1). The total number of patients who received the injections is not reported.

Effects on adjacent muscles: the incidence of partial ptosis and vertical deviation were 16% and 17% respectively. Complete ptosis was rare. In one series, slight residual ptosis (0.16%) and induced vertical deviation of greater than two prism dioptres (2%) persisted for 6 months or longer.

Retrobulbar haemorrhage (0.2%) occurred without visual loss. Decompression of the orbit after five minutes was performed to restore retinal circulation in one case.

Scleral perforation (0.11%): these tended to occur in myopic eyes and at a prior surgical site. A vitreous haemorrhage occurred in one patient which reduced vision for several months before clearing. In another patient, a reduction in vision from 20/25 to 20/30 was reported.

Pupillary dilation (0.06%): at least two of these were consistent with ciliary ganglion damage (Adie's pupil).

Past pointing and spatial disorientation may result from inducing paralysis in one or more extraocular muscles. Covering the affected eye may alleviate these symptoms.

Diplopia is common after treatment in patients with good vision in both eyes. Diplopia in adults can be managed by patching. In one case, diplopia appeared to be permanent due to loss of suppression.

No systemic paralytic effect has been seen or suspected in any patient treated with the small doses used for strabismus.

Variation in incidence rates of the most frequently observed effects, ptosis and vertical deviation per patient, have also been reported in other retrospective observational studies. There is no obvious explanation for the substantial variation. In the literature, 3 different studies (2-4) evaluating BOTOX® for the treatment of strabismus (n=266) indicated percent incidence of ptosis occurred in a range of 30% to 37% of injections or 37% of patients. Vertical deviation was reported in 42% of injections or from 10% to 34% of patients.

Other studies have shown side effects such as sub-conjunctival and conjunctival haemorrhages to be fairly common. There have also been infrequent reports of headache, cycloplegia, ocular vertigo and corneal irritation. In one study, 5/45 (11.1%) patients were shown to exhibit an increase in intra-ocular pressure which was reversible.

VIIth Nerve Disorders (hemifacial spasm)
Adverse effects reported after injection of BOTOXÒ have included blurring of vision, facial droop, dizziness and tiredness, in addition to those listed above.

Focal spasticity in children two years and older
The safety of BOTOXÒ used for the treatment of focal spasticity was evaluated, from clinical studies for the treatment of dynamic equinus foot deformity, upper limb spasticity and lower limb spasticity. As is expected for any intramuscular injection procedure, localised pain, discomfort, bruising and oedema was associated with the injection in these patients. All treatment-related adverse events were mild to moderate in severity and were self-limiting.

In children treated for upper limb spasticity, the most frequently reported treatment related adverse events included local and general weakness, trigger finger, clumsiness, hypokinesia, falling and increased frequency of micturition, joint dislocation and muscle spasms. The percent of patients who experienced these events at least once during the study are summarised below:

	BOTOXÒ (n=74)
Muscular weakness, local	5.4%
Muscular weakness, general	2.7%
Trigger finger	2.7%
Clumsiness	1.4%
Falling	1.4%
Hypokinesia	1.4%
Increased frequency of micturition	1.4%
Joint dislocation	1.4%
Muscle spasms	1.4%

Other adverse events reported commonly or very commonly in these studies were convulsions, nasopharyngitis, pneumonia, vomiting and contusion.

In children treated for dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy, the adverse events most frequently reported treatment-related included falling, leg pain,

leg (local) weakness and general weakness. The percent of patients who experienced these events at least once during the study are summarised below:

	BOTOX^{Ò} (n=215)
Falling	9.3%
Leg Pain	2.3%
Weakness, local	2.3%
Weakness, general	2.3%

Falling may be attributable to a change in ankle position and gait pattern and/or local weakness. Local weakness represents the expected pharmacological action of botulinum toxin.

Other treatment-related adverse reactions reported in 1% of patients were: leg cramps, fever, knee pain, ankle pain, pain at the injection site post-treatment and lethargy. Urinary incontinence has also been reported.

In children treated for spasticity of the hip adductor muscles, there were no adverse events reported in the studies evaluated.

Focal Spasticity in Adults
The safety of BOTOX^{Ò} was evaluated in 339 unique patients who received treatment for upper limb spasticity associated with stroke in double-blind and open-label studies. In general, the majority of adverse events reported were mild to moderate in severity and were typically self-limiting.

The following events were reported as treatment related in 1 - 4% of patients and are listed in decreasing order of incidence: arm pain and hypertonia.

Fever and flu syndrome were also reported in approximately 1% of patients. The following events were reported as treatment related in less than 1% of patients and are listed in decreasing order of incidence: hyperesthesia, arthralgia, asthenia, bursitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension and pruritus.

The safety of BOTOX^{Ò} was evaluated in 82 patients who received a single treatment for lower limb spasticity associated with stroke in either a double-blind or an open-label study. The following treatment related adverse events were reported: accidental injury (1.2%), incoordination (1.2%) and paresthesia (1.2%). Adverse events reported were mild to moderate in severity.

Of the 56 patients who received BOTOX^{Ò} in the double-blind phase of the study, 44 went on to receive a second injection in the open-label study. Additional treatment related adverse reactions reported were: hypertonia (4.5%), asthenia (2.3%), headache (2.3%) and hyperkinesia (2.3%).

Cervical Dystonia (spasmodic torticollis)

The following adverse events were reported following BOTOX® treatment for cervical dystonia. Patients received an average dose of 155 U (range 100 – 300 U).

ADVERSE EVENT	BOTOX® (n = 131)
Body as a whole:	
- neck pain	5.3%
- asthenia	3.1%
- headache	1.5%
- pain at injection site	1.5%
Digestive system	
- dysphagia	12.2%
Muscular system	
- muscle weakness	0.8%

Dysphagia was the most commonly reported adverse event after treatment with BOTOX®. Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX® resulting from the spread of the toxin outside the injected muscles. Dysphagia is usually reported as mild to moderate severity in most patients. However, in an occasional patient it may be associated with more severe problems. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. (See **Precautions**).

Neck pain due to BOTOX® injection may be due to a change in resting tone for the contralateral muscles, or other muscles not previously affected by dystonia. In rare instances, neck pain has been severe. Dysphonia has also been reported in the literature for patients who have been treated for cervical dystonia. Rhinitis has also been reported.

Primary Hyperhidrosis of the Axillae

The safety of BOTOX® was evaluated in 287 patients who received at least 1 treatment exposure of primary hyperhidrosis of the axillae in double-blind and open-label studies. Adverse events reported as treatment related in greater than 1% of BOTOX®-treated patients are listed in decreasing order of incidence: perceived increase in non-axillary sweating (4.5%), injection site pain (1.7%), pain (1.4%) and vasodilation (hot flushes) (1.0%). Two of 207 subjects (1.0%) who received repeated injections of BOTOX® developed transient arm weakness. Body odour has also been reported.

Spasmodic Dysphonia

In the largest series reported of BOTOX® treatment for this disorder common adverse events after treatment with BOTOX® were breathy dysphonia (47.6% of all treatment sessions), dysphagia (14.9%) and aspiration (5.9%) for adductor spasmodic dysphonia and dysphagia (11.2%) and stridor (6.9%) for abductor dysphonia.

In another large trial of 169 patients with spasmodic dysphonia, the following adverse events were recorded in ≥1 of 1093 BOTOX® treatments. Paralytic dysphonia (breathy dysphonia) in 338/1093 (31%) treatments (mild 139, moderate 114, severe 73, very severe 12), technical failure in 90/1093 (8%) treatments, dysphagia in 38/1093 (3%) treatments

(mild 17, moderate 15, severe 4, very severe 2), pain in 13/1093 (1%) treatments (mild 5, moderate 6, severe 2), gagging in 6/1093 (0.5%) treatments (mild 3, moderate 3), diplophonia in 3/1093 treatments, flu-like symptoms in 2/1093 treatments of moderate severity, and persistent cough in 2/1093 treatments.

Glabellar Lines
Safety of BOTOX^{Ò} for the treatment of glabellar lines was evaluated in two multicentre, double-blind, placebo-controlled, parallel-group studies (n=535; 405 in the BOTOX^{Ò}-treated group and 130 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were transient. The most frequently reported treatment related adverse events were headache (9.4% in the BOTOX^{Ò} group and 12.3% in the placebo group) and blepharoptosis (3.2% in the BOTOX^{Ò} group and 0% in the placebo group). Blepharoptosis is consistent with the pharmacologic action of BOTOX^{Ò} and may be injection technique-related.

Adverse events reported as treatment related in 1-3% of BOTOX^{Ò}-treated patients, listed in decreasing order of incidence were: injection site pain/burning/stinging (2.5%), face pain (2.2%), erythema (1.7%), local muscle weakness (1.7%), injection site oedema (1.5%), ecchymosis (1.0%), skin tightness (1.0%), paresthesia (1.0%) and nausea (1.0%).

Crow's Feet
The safety of BOTOX® for the treatment of crow's feet was evaluated in two multicentre, double-blind, placebo-controlled, parallel group studies (246 in the BOTOX^{Ò}-treated groups (6 U to 18 U/side) and 80 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were transient. The most frequently reported treatment-related adverse events were injection site haemorrhage i.e. bruising at the injection site (8.1% in the BOTOX^{Ò} 6 U to 18 U/side groups and 10.0% in the placebo group) and headache (3.7% in the BOTOX^{Ò} 6 U to 18 U/side groups and 2.5% in the placebo group). Flu syndrome was reported in 1.6% of BOTOX®-treated patients (6 U to 18 U/side) and in none of the placebo-treated patients. All other adverse events reported as treatment-related in the BOTOX® groups were reported in less than 1% of patients.

Other studies have reported the incidence of injection site bruising to be between 4-25% of BOTOX®-treated patients, with similar rates noted for placebo. Other adverse events related to BOTOX® treatment included temporary droop of the lateral portion of the lower eyelid (5%), which is consistent with the pharmacologic action of BOTOX^{Ò} and may be injection technique-related.

Forehead Lines
In a clinical study where BOTOX® was administered to 59 patients with horizontal forehead lines (8 U to 24 U into frontalis), the following treatment related adverse events were reported: headache (22.0%), bruising (10.2%), eyebrow ptosis (10.2%), eyelid swelling (20.3%), aching/itching forehead (5.1%), nausea (3.4%), feeling of tension (1.7%), flu-like symptoms/cold (1.7%) and other (6.8%). All adverse events were mild or moderate in severity and no serious adverse events were reported.

Post-marketing Experience
There have been rare spontaneous reports of death, sometimes associated with dysphagia,

pneumonia, and/or other significant debility, after treatment with BOTOX^{Ò}.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including skin rash, urticaria, soft tissue oedema, and dyspnoea (See **PRECAUTIONS**).

There have also been rare 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.

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 the **PRECAUTIONS** and **ADVERSE EFFECTS** sections: denervation/muscle atrophy; respiratory depression and/or respiratory failure (non-Cosmetic indications); dyspnea; aspiration pneumonia (non-Cosmetic indications); dysarthria; dry mouth; strabismus; peripheral neuropathy, abdominal pain; diarrhoea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance, hypoacusis; tinnitus; vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoaesthesia; malaise; myalgia; myasthenia gravis; paraesthesia; rash; erythema multiforme; pruritus; dermatitis psoriasiform; hyperhidrosis; and alopecia including madarosis.

DOSAGE AND ADMINISTRATION

Route of Administration

Intramuscular injection. Reconstituted BOTOX^{Ò} is injected with the purpose of reaching the motor endplate region of the muscle to be treated. May be subcutaneous for blepharospasm. Intradermal for primary hyperhidrosis of the axillae.

General

BOTOX^{Ò} should only be given by physicians with the appropriate qualifications and experience in the treatment of patients and the use of required equipment.
The product is for single use in one patient during one session only because the product and diluent do not contain a preservative. Once opened and reconstituted, store in the refrigerator and use within twenty four hours. Discard any remaining solution. Do not freeze reconstituted BOTOX^{Ò}.

In general, dosing of BOTOX^{Ò} should be individualised for each patient and always start with the minimal effective dose. The dosing interval should typically not be more frequent than every three months.

If different vial sizes of BOTOX^{Ò} are being used as part of one injection procedure, care

should be taken to use the correct amount of diluent when reconstituting a particular number of units per 0.1 ml. The amount of diluent varies between BOTOX^{Ò} 100 Allergan Units and BOTOX^{Ò} 200 Allergan Units. Each syringe should be labelled accordingly.

Bladder Dysfunction
The intradetrusor administration of BOTOX® is only to be conducted by a urologist/urogynaecologist who has been trained in this highly specialised technique or by a urologist/urogynaecologist under the direct supervision of a urologist/urogynaecologist who has been so trained.

Patients should not have a urinary tract infection at the time of treatment. Prophylactic antibiotics, except aminoglycosides, (see **Interactions with other Medicines**) should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment.

It is recommended that patients discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Overactive Bladder
An intravesical instillation of diluted local anaesthetic with or without sedation may be used prior to injection, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX®, as 0.5 mL (5 Units) injections across 20 sites in the detrusor, which is also the maximum recommended dose.

The recommended dilution is 100 Units/10 mL with 0.9% non-preserved saline solution (see **Dilution Table**). Dispose of any unused saline.

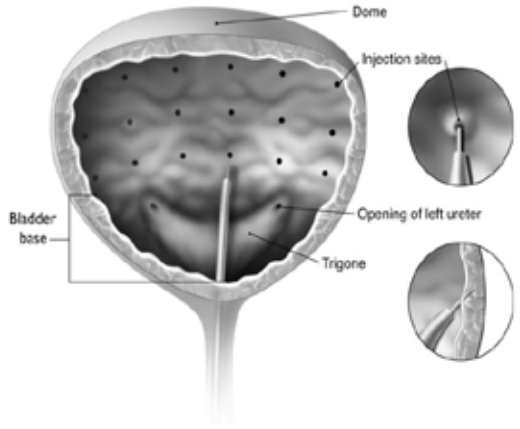
Reconstituted BOTOX® (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone and bladder base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX® prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see figure below). For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualization should not be drained so that patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Clinical improvement may occur within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 166 days [~24 weeks]), but no sooner than 3 months from the

prior bladder injection.



Neurogenic Detrusor Overactivity
An intravesical instillation of diluted local anaesthetic with or without sedation, or general anaesthesia, may be used prior to injection, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 U of BOTOX®.

Reconstitute a 200 Unit vial of BOTOX® with 6 mL of 0.9% non-preserved saline solution and mix the vial gently. Draw 2 mL from the vial into each of three 10 mL syringes. Complete the reconstitution by adding 8 mL of 0.9% non-preserved saline solution into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitute two 100 Unit vials of BOTOX®, each with 6 mL of 0.9% non-preserved saline solution and mix the vials gently. Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe. Complete the reconstitution by adding 6 mL of 0.9% non-preserved saline solution into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX® (200 U/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 U) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see

figure above). For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained. The patient should be observed for at least 30 minutes post-injection.

Clinical improvement generally occurs within 2 weeks. It is not recommended that patients be retreated pre-emptively, at fixed intervals. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 256-295 days (36-42 weeks) for BOTOX® 200 U), but no sooner than 3 months from the prior bladder injection.

Limited data is available beyond two treatments so the decision to perform a second treatment should be made only after considering the risks and benefits.

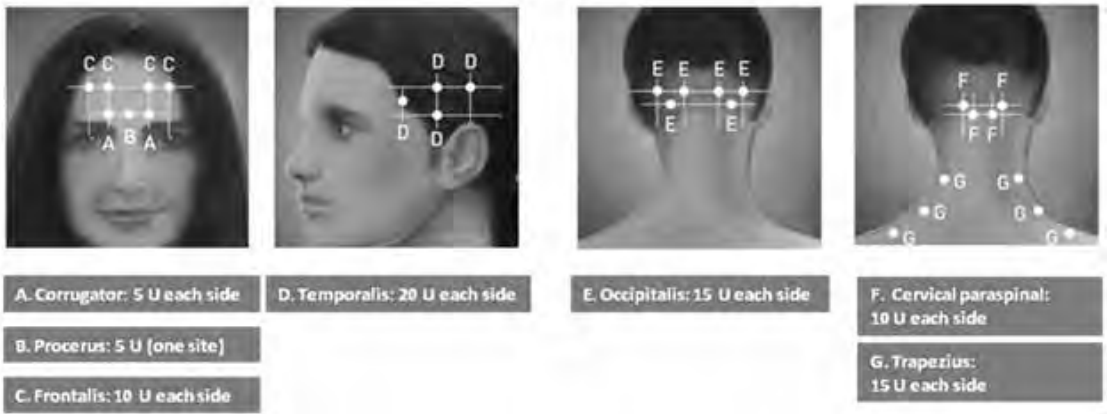
Chronic Migraine

The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 U) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the table below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated below, with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table below.

The recommended re-treatment schedule is every 12 weeks.

Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with BOTOX^{Ò} should be evaluated by a neurologist or pain management specialist prior to receiving treatment with BOTOX^{Ò}. The use of BOTOX^{Ò} for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles over 32 weeks. No long term safety or efficacy data for this indication are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

Recommended injection sites for chronic migraine:



BOTOX® Dosing By Muscle for Chronic Migraine

	Recommended Dose
Head/Neck Area	**Total Number of Units (U) (number of IM injection sites[a])**
Frontalis[b]	20 U (4 sites)
Corrugator[b]	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis[b]	30 U (6 sites) up to 40 U (up to 8 sites)
Temporalis[b]	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius[b]	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical Paraspinal Muscle Group[b]	20 U (4 sites)
Total Dose Range:	**155 U to 195 U**

[a] 1 IM injection site = 0.1 mL = 5 U BOTOX®
[b] Dose distributed bilaterally for minimum dose

Blepharospasm
An injection of BOTOX^{Ò} (botulinum toxin type A) purified neurotoxin complex 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 injection needle, preferably a 1½", 27-30 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^{Ò}.

For blepharospasm, diluted BOTOX^{Ò} injection (see Dilution Table) is injected using a 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. Pre-tarsal injections are often appropriate and may vary based on the patient's presentation. In the upper lid, maximising the distance of the injection from the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis may occur easily in the soft eyelid tissues. This may be reduced by applying light pressure at the injection site immediately after the injection.

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 as needed. 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 a minimal increase in benefit from injecting more than 5.0 U per site. Some tolerance may be found when BOTOX^{Ò} is used in treating blepharospasm if treatments are given any more frequently than every three months. The effect is rarely permanent.

The cumulative dose of BOTOX^{Ò} in a two month period should not exceed 200 U.

Strabismus
BOTOX® is intended for injection into extraocular muscles utilising 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.

To prepare the eye for BOTOX® injection, it is recommended that several drops of a local anaesthetic 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 – 0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX® (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. Overcorrections 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 stabilise the alignment.

I. Initial doses in units. 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 dioptres: 1.25 – 2.5 U in any one muscle.
   B. For horizontal strabismus of 20 prism dioptres to 50 prism dioptres: 2.5 – 5.0 U in any one muscle.
   C. For persistent sixth nerve palsy of one month or longer duration: 1.25 – 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 two-fold compared to the previously administered dose.
D. Subsequent injections should not be administered until the effects 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 one muscle is 25 U.

VIIth Nerve Disorders (hemifacial spasm)
Patients with hemifacial spasm or VIIth nerve disorder should be treated as for unilateral blepharospasm. Further injections may be necessary into the corrugator, zygomaticus major, orbicularis oris and/or other facial muscles according to the extent of the spasm. Electromyographical control may be useful to identify small circumoral muscles.

The cumulative dose of BOTOX^{Ò} in a two-month period should not exceed 200 U.

Treatment of focal spasticity of the upper limb and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years and older

The exact dosage and number of injection sites should be tailored to the child's needs based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials the dose per muscle ranged from 0.5-2.0 U/kg body weight in the upper limb and 2.0 -4.0 U/kg/body weight in the lower limb per treatment session. For the treatment of equinus foot deformity the total dose is up to 4 U/kg or 200 U (whichever is the lesser amount) divided into two sites in each medial and lateral head of the gastrocnemius muscle. In other muscles the dose per muscle ranged from 3.0-8.0 U/kg body weight and did not exceed 300U divided among selected muscles at any treatment session. Following initial injection to the gastrocnemius muscle, further involvement of the anterior or posterior tibialis may need to be considered for additional improvement in the foot position at heel strike and during standing.

A 27 or 30 gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes, but typically not more frequently than every three months. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX^{Ò} and muscles to be injected.

The table below is intended to give dosing guidelines for injection of BOTOX^{Ò} in the treatment of focal spasticity in children aged 2 years and older. The maximum cumulative dose should generally not exceed 8.0 units/kg body weight and up to a maximum of 300 U divided among selected muscles at any treatment session or in a 3 month interval:

Muscles in upper limb	**Dosage in U/kg/muscle**
Biceps brachii	0.5 - 2.0 U
Brachialis	0.5 - 2.0 U
Brachioradialis	0.5 - 2.0 U
Flexor carpi ulnaris	0.5 - 2.0 U
Flexor carpi radialis	0.5 - 2.0 U
Pronator teres	0.5 - 2.0 U
Pronator quadratus	0.5 - 2.0 U
Flexor digitorum profundus	0.5 - 2.0 U
Flexor digitorum sublimis	0.5 - 2.0 U
Flexor pollicis longus	0.5- 2.0 U
Flexor pollicis brevis	0.5 - 2.0 U
Opponens pollicis	0.5 - 2.0 U
Adductor pollicis	0.5 - 2.0 U
Muscles in lower limb	**Dosage in U/kg/muscle**
Hip adductor group (adductor longus, adductor brevis, adductor magnus, medial hamstrings)	4.0 U
Gastrocnemius	2.0-4.0 U

Focal Spasticity in Adults

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials, the doses did not exceed 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) at any treatment session. Clinical improvement in muscle tone generally occurs within two weeks following treatment with the peak effect seen four to six weeks following treatment. In clinical studies, patients were reinjected at 12- to 16-week intervals. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX^{Ò} and muscles to be injected.

The table below is intended to give dosing guidelines for injection of BOTOX^{Ò} in the treatment of focal spasticity.

Muscle	**Total Dosage; Number of Sites**
Biceps brachii	100 – 200 U; up to 4 sites
Flexor digitorum profundus	15 - 50 U; 1-2 sites
Flexor digitorum sublimis	15 - 50 U; 1-2 sites
Flexor carpi radialis	15 - 60 U; 1-2 sites
Flexor carpi ulnaris	10 - 50 U; 1-2 sites
Adductor pollicis	20 U; 1-2 sites
Flexor pollicis longus	20 U; 1-2 sites
Posterior tibialis	70 – 100 U; 1-2 sites
Soleus	80 – 125 U; 1-2 sites
Flexor digitorum longus/brevis	50 – 100 U; 2-4 sites
Gastrocnemius medial/lateral	50 – 200 U; 2-4 sites

A 27 or 30 gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

Multiple injection sites may allow BOTOX^{Ò} to have more uniform contact with the innervation areas of the muscle and may be especially useful in larger muscles.

Cervical Dystonia (spasmodic torticollis)
Dosing must be tailored to the individual patient based on the patient's head and neck position, localisation of pain, muscle hypertrophy, patient's bodyweight, and patient response.

Multiple injection sites allow BOTOX^{Ò} to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated. The treatment of cervical dystonia typically may include, but is not limited to, injection of BOTOX^{Ò} into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s).

A 25, 27 or 30 gauge needle should be used for superficial muscles and a needle of appropriate length should be used for deeper musculature. For cervical dystonia, localisation of the involved muscles with electromyographic guidance may be useful.

The table below is intended to give dosing guidelines for injection of BOTOX^{Ò} in the treatment of cervical dystonia.

Dosage Guide

Classification of Cervical Dystonia	Muscle Groupings	Total Dosage; Number of Sites
Type I Head rotated toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Splenius capitis Trapezius	50-100 U; at least 2 sites 50 U; 1-2 sites 25-50 U; 1-2 sites 25-75 U; 1-3 sites 25-100 U; 1-8 sites
Type II Head rotation only	Sternocleidomastoid	25-100 U; at least 2 sites if >25 U given
Type III Head tilted toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Trapezius	25-100 U; at posterior border; at least 2 sites if >25 U given 25-100 U; at least 2 sites 25-75 U; at least 2 sites 25-100 U; 1-8 sites
Type IV Bilateral posterior cervical muscle spasm with elevation of the face	Splenius capitis and cervicis	50-200 U; 2-8 sites, treat bilaterally

This information is provided as guidance for the initial injection. The extent of muscle

hypertrophy and the muscle groups involved in the dystonic posture may change with time necessitating alterations in the dose of toxin and muscles to be injected. The exact dosage and sites injected must be individualised for each patient.
Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Treatment intervals of less than two months are not recommended. The duration of therapeutic effect reported in the clinical trials showed substantial variation (from 2 to 32 weeks), with a typical duration of approximately 12 to 16 weeks, depending on the patient's individual disease and response.

The table below shows the median dose of BOTOX^{Ò} injected per muscle in a clinical study in which dose was determined by the practitioner based on the presentation of the individual cervical dystonia patient.

Muscle(s)	**Range of Medians* (U)**	**Minimum-Maximum Dose, U/muscle****
Sternocleidomastoid	50	15-190
Trapezius	50-60	5-200
Levator scapulae	50	10-180
Splenius capitis/cervicis	90	10-240
Scalene	40	5-90

* Two medians were given: for those patients who received one injection cycle (n=121) and for those patients who received two injection cycles (n=90). When only one number is given, the medians were the same for both groups of patients.

** Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia (See **Precautions**).

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of BOTOX^{Ò} ranged from 140 to 280 U. In more recent studies, the doses have ranged from 95 to 360 U (with an approximate mean of 240 U). As with any drug treatment, initial dosing should begin at the lowest effective dose.

In general, a total dose of 360 U every two months should not be exceeded for the treatment of cervical dystonia. The time-to-retreatment will vary between patients, however data from controlled clinical studies indicates that symptoms may start to re-emerge at approximately 8-10 weeks post-injection (see **Pharmacology – Clinical Trials**).

Repeat doses should be administered when the clinical effect of a previous injection diminishes, though usually not more frequently than every two months. "Booster" injections are not recommended.

Primary Hyperhidrosis of the Axillae
For the treatment of hyperhidrosis, 100 U of BOTOX^{Ò} should be reconstituted with 4.0 mLs of sterile 0.9% sodium chloride for injection. For each axilla, 50 U of BOTOX^{Ò} (2.0 mL) should be injected intradermally and evenly distributed in 10-15 sites approximately 1-2 cm apart within the hyperhidrotic area. For the treatment of hyperhidrosis, a 30 gauge needle should be used. The hyperhidrotic area may be defined using standard staining techniques (e.g Minor's iodine starch test). Each dose is injected to a depth of approx. 2 mm and at a 45 degree angle to the skin surface with the bevel side up to minimise leakage and ensure the

injections remain intradermal. Repeat injections for axillary hyperhidrosis should be administered when the effects from the previous injection subside. However, repeat injections at intervals of less than four months are not recommended.

Spasmodic Dysphonia

Patients with spasmodic dysphonia should be treated by physicians skilled in the anatomy and physiology of the larynx, and have facility with nasal endoscopy and also electromyographically guided injections. The procedure should be carried out in a facility equipped to manage potential acute complications such as reflex stridor. The treatment program should be individualised for each patient at each treatment session. Peak effect is generally seen within 7 days following an injection.

BOTOX® (100 U/vial) should be reconstituted with 4.0 to 5.0 mL of 0.9% sterile non-preserved saline, giving a final concentration of 2.0–2.5 units per 0.1 mL. It is usual to commence with a standard dose of 1.0–2.5 units in 0.1 mL of BOTOX® to each thyroarytenoid muscle in adductor spasmodic dysphonia and subsequently vary the dose by altering the concentration according to patient requirements and response to therapy. An occasional patient will require 3 units per vocal cord and many patients over the years have reduced their dose, down to even 0.2 units per vocal cord. Bilateral injections are generally recommended but an occasional patient will benefit from unilateral injections, sometimes alternating between sides with each subsequent treatment.

In abductor spasmodic dysphonia 2-5 units of BOTOX® are usually injected unilaterally into one posterior cricoarytenoid muscle via a lateral retrocricoid, supracricoid or transcricoid approach.

The injection is usually performed in the supine position with a small pillow under the shoulders to improve laryngeal exposure. For adductor spasmodic dysphonia, the laryngeal surface landmarks are identified, including the thyroid and cricoid cartilage, and in particular the small gap of the cricothyroid membrane. Identification of the landmarks is a critical part of this procedure and sometimes this can be difficult in individuals with thick necks.

In adductor spasmodic dysphonia the EMG recording needle is advanced in the midline through the cricothyroid membrane, directing the needle rostrally, and approximately 30^{o} laterally towards the intented thyroarytenoid muscle. For a bilateral procedure, the needle is redirected towards the corresponding contralateral muscle. Once within the muscle, EMG insertional activity is audible and placement can be confirmed by having the patient phonate an ”e”. Having confirmed needle placement, the desired amount of BOTOX® in 0.1 mL is injected.

In all cases of abductor spasmodic dysphonia, endoscopy should be performed prior to each treatment to assess the dynamic activity of each vocal cord and the size of the glottal airway. Typically, the posterior cricoarytenoid (PCA) muscle on the more active side is chosen for therapy. A retrocricoid approach should be used whereby the injection needle, containing 2-5 units of BOTOX® in 0.1 mL, is directed towards the PCA muscle in a curving fashion at the level of the cricoid cartilage to lie behind the larynx. The larynx may be rotated laterally on the appropriate side to improve access. To confirm needle placement, the patient sniffs sharply to activate the posterior cricoarytenoid muscle resulting in a characteristic EMG

interference pattern. BOTOX® is then injected. Only unilateral injections are recommended at each treatment session. The determination of which PCA muscle to treat at any injection session is determined by endoscopic review. Treatment sessions are performed only when the non-injected cord has sufficient motion to protect from stridor in the event that the injected cord would become immobile. An occasional patient with abductor spasmodic dysphonia will have increased activity of the cricothyroid muscle, which can also be evaluated by EMG, and may also benefit from supplemental injections into this muscle.

To date there has only been one report of a patient developing resistance to the injections, with the development of neutralising antibodies, probably because the doses used are very small compared to other indications.

Upper Facial Lines (Glabellar Lines, Crow's Feet and Forehead Lines)
As optimum dose levels and number of injection sites per muscle may vary among patients, individual dosing regimes should be drawn up. The recommended injection volume per injection site is 0.1 mL.

Glabellar Lines
BOTOX^{Ò} should be reconstituted with 0.9% sterile non-preserved saline (100 U/2.5 mL) and injected using a sterile 30 gauge needle. A volume of 0.1 mL (4 U) is administered in each of 5 injection sites, 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 U.

In order to reduce the complication of ptosis, injection near the levator palpebrae superioris muscle should be avoided, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

Improvement of severity of glabellar lines generally occurs within one week after treatment. The effect was demonstrated for up to 4 months.

Crow's Feet
BOTOX® should be injected bilaterally at 3 sites in the lateral aspect of the orbicularis oculi (i.e. total of 6 injections), where most lines are seen when a smile is forced. In general, 2-6 U is recommended per injection site at a 2-3 mm depth, for a total dose of 6-18 U per side.

Injections should be at least 1 cm outside the bony orbit, not medial to the vertical line through the lateral canthus and not close to the inferior margin of the zygoma.

Forehead Lines
BOTOX® should be injected intramuscularly at each of 4 injection sites in the frontalis muscle. In general, 2-6 U is recommended per injection site every 1-2 cm along either side of a deep forehead crease, for a total dose of 8-24 U.

Injections should be at least 2-3 cm above the eyebrow to reduce the risk of brow ptosis.

Dilution Technique
It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. To reconstitute vacuum-dried BOTOX^{Ò} injection, 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^{Ò} 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^{Ò} should be administered within 24 hours after reconstitution in the vial.

During this time period, reconstituted BOTOX^{Ò} should be stored in a refrigerator (2°C to 8° C). Reconstituted BOTOX^{Ò} should be clear, colourless to slightly yellow and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration and whenever the solution and the container permit.

Dilution Table for 50 U, 100 U and 200 U vials:

Diluent Added (0.9% Sodium Chloride Injection)	50 U Vial	100 U Vial	200 U Vial
	Resulting dose (U/0.1 mL)	Resulting dose (U/0.1 mL)	Resulting dose (U/0.1 mL)
0.5 mL	10	20	40
1 mL	5	10	20
2 mL	2.5	5	10
4 mL	1.25	2.5	5
5 mL	N/A	2	4
8 mL	N/A	1.25	2.5
10 mL	N/A	1	2

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX^{Ò} 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).

For reconstitution technique for intradetrusor injections for neurogenic detrusor overactivity, please refer to Dosage and Administration section under heading Neurogenic Detrusor Overactivity.

Lack of Response

In the absence of the desired effect after the first treatment session, i.e. no significant clinical improvement from baseline by one month after injection, the following actions should be considered:

- Analysis of potential causes of lack of effect, e.g. inappropriate selection of muscles to be injected; insufficient dose; poor injection technique; muscles inaccessible to injection; underlying structural abnormalities; such as muscle contractures or bone disorders; relative weakness of antagonist muscles; change in pattern of muscle involvement; patient perception of benefit compared with initial results; inappropriate storage or reconstitution; and/or formation of toxin-neutralising antibodies.
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A.

For the second treatment session, in the absence of any undesirable effects after the first

treatment session, the physician should consider the following:
- adjust the dose, taking into account the analysis of the earlier treatment failure;
- use of EMG guidance as appropriate; and
- maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections, taking into account dosage adjustments and targeting of injections, alternative treatment methods should be considered.

A neutralising antibody is defined as an antibody that inactivates the biological activity of the toxin. In general, the proportion of patients who lose their response to botulinum toxin therapy and have demonstrable levels of neutralising antibodies is less than 5%, though in a long-term juvenile cerebral palsy study, of 117 patients treated with BOTOX^{Ò}, antibodies were detected in 33/117 (28%) at either 27 or 39 months. Thirty-one of these 33 had been responders, 19/31 (6%) continued to respond, with 7/31 (2%) becoming non-responders, and no data available for 5/31.

In the pivotal studies, none of the 615 overactive bladder patients with analysed specimens developed the presence of neutralizing antibodies.

In the pivotal studies, none of the 475 neurogenic detrusor overactivity patients with analysed specimens developed the presence of neutralising antibodies.

The critical factors for neutralising antibody production are the frequency and dose of injection. Tolerance may be observed in some patients treated more frequently than every three months. The potential for neutralising antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections (injection intervals should typically be no more frequent than three months). The dose should not exceed 360 U in any two month period for adult spasticity patients and patients with cervical dystonia. In treating paediatric patients, the maximum cumulative dose should generally not exceed 8 U/kg, up to a maximum of 300 U, in a 3 month interval. More than one ineffective treatment course should occur before classification of a patient as a non-responder, because there are patients who continue to respond to therapy despite the presence of neutralising antibodies.

OVERDOSAGE

Overdose of BOTOX^{Ò} is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are likely not to be apparent immediately post-injection. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis. Local weakness is usually well tolerated and resolves spontaneously without intervention. However, dysphagia may result in loss of airway protection and aspiration pneumonia.

The entire contents of a vial is below the estimated dose (from primate studies) for toxicity in humans weighing 6 kg or greater.

Should symptoms (muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing or

respiratory depression) occur post injection or oral ingestion, the person should be medically monitored for up to several weeks. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalisation. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur. Specific anti-toxin to botulinum toxin is only likely to be effective if given within thirty minutes of the botulinum toxin injection.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

BOTOX^{Ò} (botulinum toxin type A) purified neurotoxin complex is a sterile, vacuum-dried preparation. It is supplied in a clear glass vial with a rubber stopper and tamper-proof aluminium seal, containing a white powder for reconstitution. BOTOX^{Ò} is available in 50U, 100 U and 200 U of vacuum-dried *Clostridium botulinum* toxin type A. Refer to description for list of excipients.

Storage

Store the vacuum-dried product in the refrigerator between 2°C to 8°C.

Administer BOTOX^{Ò} (botulinum toxin type A) purified neurotoxin complex within 24 hours after the vial is removed from the refrigerator and reconstituted. During these twenty four hours, reconstituted BOTOX^{Ò} should be stored in a refrigerator (2°C to 8°C). If reconstituted BOTOX® is further diluted in a syringe for intradetrusor injections, it should be used immediately. Reconstituted BOTOX^{Ò} should be clear, colourless or slightly yellow and free of particulate matter.

The reconstituted product does not contain a preservative. It should be used for one patient only and any residue discarded.

Disposal

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste. Unused vials should be reconstituted with a small amount of water and then autoclaved. Any unused vials or equipment (such as syringes) should be autoclaved (120^{o}C for 30 minutes), or the residual BOTOX^{Ò} inactivated using dilute hypochlorite solution (0.5% or 1%) for five minutes and then disposed of as medical waste.

NAME AND ADDRESS OF THE SPONSOR

Allergan Australia Pty Ltd
810 Pacific Highway
Gordon NSW 2072
A.B.N. 85 000 612 831

BOTOX^{Ò} 50 U* - AUST R 195530
BOTOX^{Ò} 100 U - AUST R 67311

BOTOX^{Ò} 200 U - AUST R 172264
*- not marketed

POISON SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine

DATE OF APPROVAL
Date of approval: 06 August 2013
Date of most recent amendment: 12 December 2011