



Botulinum Toxins Therapeutic Class Review (TCR)

May 30, 2015

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
abobotulinumtoxinA (Dysport®) ¹	Ipsen Biopharm	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults < 65 years of age
incobotulinumtoxinA (Xeomin®) ²	Merz	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients Treatment of blepharospasm in adults previously treated with onabotulinumtoxinA (Botox) Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and/or corrugator muscle activity in adults
onabotulinumtoxinA (Botox®) ³	Allergan	Treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain in patients 16 years and older Treatment of upper limb spasticity in adults to decrease the severity of increased muscle tone in elbow, wrist, finger, and thumb flexors. Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adults Treatment of blepharospasm associated with dystonia in patients 12 years and older Treatment of strabismus in patients 12 years and older Prophylaxis of headaches in adults with chronic migraine (defined as 15 or more days/month with headache duration of at least 4 hours) Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication Treatment of overactive bladder (OAB), with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
onabotulinumtoxinA (Botox® Cosmetic) ⁴	Allergan	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults less than or equal to 65 years Temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adults less than or equal to 65 years
rimabotulinumtoxinB (Myobloc®) ⁵	Solstice Neurosciences	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain

OVERVIEW

Cervical dystonia, also known as spasmodic torticollis, is a painful, localized neurologic movement disorder. Symptoms are caused by intermittent or sustained contractions of the neck muscles that control the position of the head. Head position is altered, and the effect can spread down to the shoulders. Head or arm tremor can also be experienced. Botulinum toxins are a common treatment for this disorder. The ability to administer botulinum toxins directly to the affected area(s) makes these products a logical first option. Other therapeutic options include dopamine agonists. Pharmaceutical-grade botulinum toxins are purified and are dosed well below amounts that could cause botulism in patients.

Glabellar lines are the vertical lines between the eyebrows that result from frowning. This is due to the repeated contraction of the corrugator and procerus muscles. As humans age, the skin loses its elasticity, resulting in these wrinkles. Lateral canthal lines (crow's feet) are the radial lines which form at the corners of the eyes. For patients who seek cosmetic enhancement of these features, botulinum toxin injections are effective.

Other conditions resulting from increased neuromuscular activity for which botulinum toxins are treatment options include muscle spasticity, excessive armpit sweating (axillary hyperhidrosis), eyelid twitching (blepharospasm), and improper eye alignment (strabismus).

In August 2011, the Food and Drug Administration (FDA) approved onabotulinumtoxinA (Botox) injection to treat urinary incontinence in people with neurologic conditions, such as spinal cord injury and multiple sclerosis, who have overactivity of the bladder. Uninhibited urinary bladder contractions in people with some neurological conditions can lead to an inability to store urine. Current management of this condition includes medications to relax the bladder (anticholinergics) and use of a catheter to regularly empty the bladder. The treatment consists of onabotulinumtoxinA being injected into the bladder via cystoscopy, which may require general anesthesia, resulting in relaxation of the bladder, an increase in its storage capacity, and a decrease in urinary incontinence. The duration of the effect of onabotulinumtoxinA on urinary incontinence in patients with bladder overactivity associated with a neurologic condition is up to ten months.⁶

In January 2013, the FDA indication expanded onabotulinumtoxinA to include the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency. Current treatment options are very similar for the two conditions.⁷ However, OAB has preliminary options of bladder training and pelvic floor exercises, followed by anticholinergics and, as a last resort, surgery (bladder augmentation). A similar cystoscopic procedure is employed, with or without anesthesia; onabotulinumtoxinA is injected into the detrusor muscle via a cystoscope. The duration of the effect of onabotulinumtoxinA on OAB is approximately 24 weeks, but no sooner than 12 weeks prior to the last bladder injection.⁸

This review will focus on the non-cosmetic use of agents in this class.

PHARMACOLOGY^{9,10,11,12,13}

Botulinum toxins inhibit the release of acetylcholine from peripheral cholinergic nerve endings. This occurs via binding of toxins to specific surface receptors on nerve endings. The toxins enter nerve terminals and cause intracellular blockage of neurotransmitter activity. Thus, conditions characterized by excessive nervous activity are therapeutically altered. Following administration, the muscle may atrophy; however, re-innervation of the muscle may occur, slowly reversing muscle denervation.

PHARMACOKINETICS^{14,15,16,17,18}

Botulinum toxins are not detectable in the peripheral blood following intramuscular injection.

CONTRAINDICATIONS/WARNINGS^{19,20,21,22,23}

Botulinum toxins are contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or their components. Patients who are allergic to cow's milk protein should not be treated with abobotulinumtoxinA (Dysport). All products are contraindicated in patients with infection at the proposed injection site.

All products in this review contain a boxed warning regarding the potential for distant spread of the toxin effect. Although effects are localized and drug is not detected in the blood, effects can be observed beyond the site of local injection. Symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysarthria, dysphoria, and urinary incontinence (symptoms reported hours to weeks after injection). In addition, treatment with botulinum toxins can result in swallowing or breathing difficulties. Patients with pre-existing conditions involving these conditions, particularly cervical dystonia and other neuromuscular disorders, may be more susceptible to complications.

Potency units are specific to each product and the assay method utilized. Therefore, products are not interchangeable, and units cannot be converted to those of any other product.

AbobotulinumtoxinA warns against use in patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in target muscles, marked facial asymmetry, inflammation at the injection site, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or the inability to substantially lessen glabellar lines by physically spreading them apart; caution should be used with these patients. Botulinum toxins can cause reduced blinking, leading to corneal exposure and ulceration.

Intradetrusor injection of onabotulinumtoxinA (Botox) is contraindicated in patients with detrusor overactivity associated with a neurologic condition who have acute urinary tract infection, and in patients with acute urinary retention who are not routinely performing clean intermittent self-catheterization (CIC). Autonomic dysreflexia associated with intra detrusor injections of onabotulinumtoxinA could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. Due to the risk of urinary retention, only those patients willing and able of catheterization post-treatment should be treated for bladder dysfunction.

Patients should not have an acute urinary tract infection (UTI) prior to treatment with intradetrusor injections of onabotulinumtoxinA. UTI incidence is increased by the use of onabotulinumtoxinA in treating patients with OAB. Two specific populations should be assessed prior to beginning treatment; patients with two or more UTIs in the past six months and those taking antibiotic prophylaxis due to recurrent UTIs. Therapy should only be considered when the benefit would outweigh the potential risk.

These products contain human albumin and, therefore, carry a remote risk for transmission of viral diseases.

Risk Evaluation and Mitigation Strategies (REMS)²⁴

Previous REMS requirements were released from the following products in 2012; Dysport: May 2012, Myobloc: June 2012, and Botox and Xeomin: July 2012.

DRUG INTERACTIONS^{25,26,27,28,29}

No formal drug interaction studies have been conducted with botulinum toxins. However, patients undergoing treatment concomitantly with aminoglycosides or other agents that interfere with neuromuscular transmission should be closely monitored for additive effects. The use of anticholinergic drugs following botulinum toxins may potentiate anticholinergic effects like blurred vision. The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown.

Prior to being treated with intra detrusor injections of onabotulinumtoxinA (for urinary incontinence or OAB), patients should discontinue anti-platelet therapy at least three days before the procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding.

ADVERSE EFFECTS

Drug	Injection site discomfort	Muscular weakness	Musculoskeletal pain	Dysphagia	Dry mouth	Dysphonia
abobotulinumtoxinA (Dysport) ³⁰	13 (8)	16 (4)	7 (3)	15 (4)	13 (7)	6 (2)
incobotulinumtoxinA (Xeomin) ³¹	4-9 (7)	7-11 (1)	4-7 (1)	13-18 (3)	16 (3)	nr
onabotulinumtoxinA (Botox) ³²	2-10	2-3 (0)	5-9 (4)	19	2-10	2-10
onabotulinumtoxinA (Botox Cosmetic) ³³	>1	1 (0)	2 (1)	nr	nr	nr
rimabotulinumtoxinB (Myobloc) ³⁴	12-16 (9)	3-6 (3)	6-13 (10)	10-25 (3)	3-34 (3)	nr

Adverse effects data are obtained from product package information and, therefore, should not be considered comparative or all inclusive. Adverse effect rates have been taken from different patient populations; frequency of occurrence is not representative of all patients, rather, the injection location. nr = not reported. Placebo rates are in parentheses.

The formation of neutralizing antibodies to botulinum toxins has been reported. The presence of these antibodies may reduce the effectiveness of treatment by inactivating the biological activity of the toxin. Study results suggest that frequent injections and high doses are factors which may lead to immunogenicity. Potential for antibody formation may be minimized by using the lowest effective dosing and longest interval.³⁵

The following adverse event rates with onabotulinumtoxinA (Botox) in the treatment of urinary incontinence due to detrusor overactivity were reported at any time following initial injection and prior to re-injection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), fatigue (6%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

The following adverse event rates with onabotulinumtoxinA (Botox) in the treatment of overactive bladder were reported as occurring within 12 weeks of the first intradetrusor injection: urinary tract infection (18%), dysuria (9%), urinary retention (6%), bacteriuria (4%), and residual urine volume (3%). A higher incidence of UTI was observed in patients with diabetes mellitus.

SPECIAL POPULATIONS^{36,37,38,39,40}

Pediatrics

Safety and effectiveness of abobotulinumtoxinA (Dysport) and incobotulinumtoxinA (Xeomin) in children have not been established. Safety and effective use of onabotulinumtoxinA (Botox) in the treatment of blepharospasm and strabismus in patients less than 12 years of age has not been established, nor has it been established in the treatment of cervical dystonia in patients less than 16 years of age.

Safety and effective use of onabotulinumtoxinA (Botox) in the treatment of urinary incontinence due to detrusor overactivity in patients below the age of 18 years have not been established.

Use in patients under 18 years of age is not recommended for these products in the treatment of glabellar lines, spasticity, axillary hyperhidrosis, and chronic migraine prophylaxis.

Safety and efficacy of rimabotulinumtoxinB (Myobloc) in children have not been established.

Pregnancy

All botulinum toxins are in Pregnancy Category C.

DOSAGES

Drug	Dose	Availability
abobotulinumtoxinA (Dysport) ⁴¹	Cervical dystonia: 500 units IM as a divided dose among affected muscles Doses ranging from 250 to 1000 units may be re-administered upon return of clinical symptoms.	300, 500 unit vials
incobotulinumtoxinA (Xeomin) ⁴²	Cervical dystonia: 120 units IM in divided doses, as necessary Blepharospasm: 1.25-2.5 units per injection site; if known, dose depends on previous dose of onabotulinumtoxinA (Botox); Initial total dose should not exceed 70 units for both eyes (35 units per eye)	50, 100 unit vials
onabotulinumtoxinA (Botox) ⁴³	Cervical dystonia: Number of units given IM dependant on head and neck position, divided among affected muscles (maximum 50 units/site) Upper limb spasticity: number of units dependant on affected muscle Axillary hyperhidrosis: 50 units intradermally per axilla Blepharospasm: 1.25-2.5 units into each of 3 sites per affected eye Strabismus: 1.25-2.5 units in any 1 muscle Detrusor overactivity: 200 units IM (divided into 30 1mL injections) per treatment into the detrusor muscle Overactive Bladder (OAB): 100 units (divided into 20 0.5mL injections, approximately 1 cm apart) into the detrusor muscle (avoiding the trigone) Chronic migraine prophylaxis: 155 units IM (divided) across 7 head and neck muscle sites Maximum cumulative dose in adults: Not to exceed 400 units in a 3-month interval	100, 200 unit vials
rimabotulinumtoxinB (Myobloc) ⁴⁴	Cervical dystonia: 2,500-5,000 units IM divided among affected muscles (for patients with a prior history of tolerating botulinum toxin injections). Patients without prior history should receive a lower initial dose.	2,500, 5,000, 10,000 unit vials

Doses may be repeated when clinical effects from the previous dose diminish. In general, repeat doses should not be administered more frequently than every three months.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class for approved indications. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Blepharospasm

abobotulinumtoxinA (Botox) and onabotulinumtoxinA (Dysport)

A double-blind study was performed on 212 patients with essential blepharospasm who received one injection of abobotulinumtoxinA and one injection of onabotulinumtoxinA in two separate treatment sessions.⁴⁵ Patients were randomized at the first session to one product, and then given the other product at the second session. The average dose of abobotulinumtoxinA per treatment was 45.4 units +/- 13.3 and of onabotulinumtoxinA 182.1 units +/- 55.1. An empirical ratio for Botox: Dysport of 1:4 was used in order to ensure equal doses. All patients had received botulinum toxin injections prior to the present study. The effect of abobotulinumtoxinA lasted 7.98 weeks +/- 3.8, while the effect of onabotulinumtoxinA lasted 8.03 weeks +/- 4.6. There was no statistically significant difference in the duration of the treatment effect between the two preparations (p=0.42). The rate of occurrence of ptosis was significantly lower with abobotulinumtoxinA (p<0.01). Adverse effects (ptosis, tearing, blurred vision, double vision, hematoma, foreign body sensation) were observed with abobotulinumtoxinA in 17% of the treatment sessions and with onabotulinumtoxinA in 24.1% (p<0.05). OnabotulinumtoxinA is not indicated for the treatment of blepharospasm.

Cervical Dystonia

abobotulinumtoxinA (Botox) and onabotulinumtoxinA (Dysport)

Patients with cervical dystonia were randomized to receive either the clinically indicated dose of abobotulinumtoxinA or three times that dose in onabotulinumtoxinA units.⁴⁶ Drug was administered in a double-blind fashion at one or more sites per muscle. Patients (n=73) returned for assessment two, four, eight, and 12 weeks after treatment. The Tsui scale was used for evaluation of patient outcomes. The Tsui scale is a clinician-assessed scale (range: 0 to 25) of impairment that grades the severity of postural deviance, as well as notes the presence or absence of head tremor. It also incorporates whether movements are continuous or intermittent. The mean post-treatment Tsui scores for the onabotulinumtoxinA group (4.8) and the abobotulinumtoxinA group (5.0) were not statistically different (p=0.66). Both groups showed substantial improvement in Tsui score by week two

(onabotulinumtoxinA 46%; abobotulinumtoxinA, 37%), with a peak effect at week four (onabotulinumtoxinA 49%; abobotulinumtoxinA 44%). The duration of effect, assessed by time to retreatment, was also similar (onabotulinumtoxinA 83.9 days; abobotulinumtoxinA 80.7 days; $p=0.85$). During the study, 58% of onabotulinumtoxinA patients and 69% of abobotulinumtoxinA patients reported adverse events ($p=0.35$). A global assessment of efficacy and safety considered that 76% of onabotulinumtoxinA patients and 66% of abobotulinumtoxinA patients were treatment successes ($p=0.32$).

A double-blind, randomized, three-period crossover study involving 54 patients with cervical dystonia was performed.⁴⁷ The patients received the following treatments in a randomized order: abobotulinumtoxinA at the usually effective dose, onabotulinumtoxinA at a dose of 1:3 to abobotulinumtoxinA, and at a dose of 1:4. The improvement of the Tsui and in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) pain scales between baseline and a control visit one month after each of the three injections, as well as the incidence of adverse events, was assessed. The TWSTRS scale is comprised of three subscales (Severity, Disability, and Pain) that are scored independently and then combined (range: 0 to 87) to assess the measure of impact of cervical dystonia on patients. Comparison of the Tsui scores and of the TWSTRS pain scores showed a better effect on impairment and pain with onabotulinumtoxinA 1:3 ($p=0.02$ and 0.04 , respectively) and 1:4 ($p=0.01$ and 0.02 , respectively) than with abobotulinumtoxinA. The number of adverse events was higher with both onabotulinumtoxinA treatments. The most frequent adverse event was dysphagia, found in 3, 15.6, and 17.3% (abobotulinumtoxinA, onabotulinumtoxinA 1:3, and 1:4, respectively) of the patients.

botulinum toxin A and rimabotulinumtoxinB (Myobloc)

A randomized, double-blind, parallel-arm study compared botulinum toxin type A with rimabotulinumtoxinB in 139 subjects with cervical dystonia who had a previous response from botulinum toxin type A.⁴⁸ Patients were evaluated at baseline, four weeks, eight weeks, and two-week intervals thereafter until loss of 80% of clinical effect or completion of 20 weeks of observation. Improvement in TWSTRS score was found at four weeks after injection and did not differ between serotypes. Dysphagia and dry mouth were more frequent with rimabotulinumtoxinB (dysphagia: 19 versus 48%, $p=0.0005$; dry mouth 41 versus 80%, $p<0.0001$). In clinical responders, botulinum toxin type A had a modestly longer duration of benefit (14 weeks versus 12.1 weeks, $p=0.033$).

Botulinum toxin-naïve cervical dystonia subjects ($n=111$) were randomized in a double-blind manner to botulinum toxin type A or rimabotulinumtoxinB and evaluated at baseline and every four weeks following one treatment.⁴⁹ The primary measure was the change in TWSTRS from baseline to week four post-injection. Improvement in TWSTRS-total scores four weeks after rimabotulinumtoxinB was noninferior to botulinum toxin type A (adjusted means 11.0 and 8.8, respectively). The median duration of effect of botulinum toxin type A and rimabotulinumtoxinB was not different (13.1 versus 13.7 weeks, respectively; $p=0.833$). There were no significant differences in the occurrence of injection site pain and dysphagia. Mild dry mouth was more frequent with rimabotulinumtoxinB, but there were no differences for moderate/severe dry mouth. This study was performed by the manufacturer of rimabotulinumtoxinB.

Migraine Prophylaxis

onabotulinumtoxinA (Botox)

A pair of studies assessed the efficacy, safety, and tolerability of onabotulinumtoxinA as headache prophylaxis in adults with chronic migraine.^{50,51} This phase III study was a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Subjects were randomized to onabotulinumtoxinA injections (n=341) every 12 weeks or placebo (n=338) for two cycles. The primary endpoint was mean change from baseline in headache episode frequency at week 24. No significant between-group difference for onabotulinumtoxinA versus placebo was observed for the primary endpoint, headache episodes (-5.2 versus -5.3; p=0.344). Significant between-group differences were observed for the secondary endpoints, headache days (p=0.006) and migraine days (p=0.002) for onabotulinumtoxinA. OnabotulinumtoxinA was safe and well tolerated, with few treatment-related adverse events. The second study was of a similar design and study population. The primary efficacy endpoint was mean change in headache days per 28 days from baseline to weeks 21-24 post-treatment. The difference from placebo for the primary endpoint was statistically significant for onabotulinumtoxinA (-9 versus -6.7, p<0.001). OnabotulinumtoxinA showed significant differences in all secondary endpoint comparisons and was safe and well tolerated.

Detrusor Overactivity

onabotulinumtoxinA (Botox)

Two double-blind, placebo-controlled, randomized, multicenter clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition that were either spontaneously voiding or using catheterization.⁵² A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 units of onabotulinumtoxinA (n=227), 300 units of onabotulinumtoxinA (n=223), or placebo (n=241). In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for onabotulinumtoxinA (200 Units) at the primary efficacy time point at week six. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. No additional benefit of onabotulinumtoxinA 300 units over 200 units was demonstrated.

Overactive Bladder (OAB)

onabotulinumtoxinA (Botox)

Two randomized, double-blind, placebo-controlled 24-week trials in 1,105 patients who could not tolerate or had not responded to anticholinergic therapy, were cystoscoped and received intradetrusor injections of either 100 units of onabotulinumtoxinA (administered as 20 five-unit intradetrusor injections spaced about 1 cm apart) or placebo.^{53,54} In one of the studies, which enrolled 557 patients, the mean reduction in daily frequency of urinary incontinence episodes after 12 weeks, the primary endpoint, was -2.65 with onabotulinumtoxinA and -0.87 with placebo (p<0.001). Statistically significant reductions in daily urinary incontinence episodes were also reported in the other trial. The median duration of response in both trials was 19-24 weeks with onabotulinumtoxinA and 13 weeks with placebo.

SUMMARY

All botulinum toxin products are safe and effective treatments for neuromuscular disorders. From limited comparative data, it appears that all products are equally effective for approved indications. OnabotulinumtoxinA (Botox) is at least as tolerable as the other available products based on clinical data. The increased incidences of adverse events with other botulinum toxins in clinical trials may be due to the uncertain methods of achieving equipotent doses between different products. Available data support the interchangeability of these products, although not at 1:1 dosing based on units.

A variety of treatments are available for prevention of chronic and episodic migraines. OnabotulinumtoxinA is marginally effective in preventing headache in chronic migraines.

Different treatment modalities are available for management of OAB. OnabotulinumtoxinA during cystoscopy is modestly effective in reducing OAB symptoms. It is associated with adverse events of urinary tract infections and urinary retention.

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