

## Drug Class Update: Botulinum Toxins

**Date of Review:** June 2023

**Date of Last Review:** May 2014 (Botulinum Toxins)  
May 2019 (Migraine)

**Dates of Literature Search:** 03/01/2018 - 02/23/2023

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

The purpose of this review is to evaluate the literature for new high-quality evidence for the use of botulinum toxins (BoNT) and provide an approval route for unfunded conditions that will be covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program. The Early and Periodic Screening, Diagnostic and Treatment program may allow for treatment of some conditions, for people under 21 years old who are enrolled in Medicaid, which are not normally covered under the Oregon Health Plan (OHP) fee-for-service (FFS) program.

### **Plain Language Summary:**

- The review looks for new evidence for the use of botulinum toxins for medical conditions with a particular interest in evidence for use in adolescents and children under 21 years of age.
- Botulinum toxin is used for many different reasons; however, the Oregon Health Plan only covers those disease states that use botulinum toxin for medical purposes, such as migraine headaches or leaky bladder rather than cosmetic reasons such as minimizing wrinkles. Table 1 has a list of Food and Drug Administration (FDA) approved botulinum toxin products and the conditions that are approved to treat.
- Botulinum toxin is available as two types; botulinum toxin type A and botulinum toxin type B. One of the ways these types of botulinum toxins differ is by the different conditions that they have shown that they can effectively treat.

### Conditions that botulinum toxins were shown to be effective:

- The Agency for Health Care Quality and Research reviewed the use of botulinum toxin A for the use in urinary incontinence (leaky bladder) and found that it was more effective than no treatment at curing the condition. Another review evaluated the use of botulinum toxin A in people with an increased urge to urinate and found that it was more helpful than placebo (sugar pill) in reducing these symptoms. The National Institute for Health and Care Excellence recommends the use of botulinum toxin A for adult women with leaky bladder (urinary incontinence) who have tried to take medications by mouth to decrease the number of leaks but still have symptoms.
- A review done by Cochrane Database of Systematic Reviews found that botulinum toxin B may be helpful to reduce excessive drooling in people that have a disease that affects nerve cells in the brain and spinal cord, by slightly reducing the amount of saliva production. A type of botulinum toxin, called incobotulinum toxin A, was studied by the Canadian Agency for Drugs and Technology in Health for the use in the treatment of excessive drooling when

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caused by a disorder of the nervous system. Incobotulinum toxin A was found to be better than placebo (salt water injection) to decrease drooling based on one study.

- The use of botulinum toxin A was studied for the treatment of muscle spasms in the legs of children that have cerebral palsy and was found to help more than placebo in improving the child's ability to walk.
- A report by Cochrane Systematic Reviews found that for people that have unwanted muscle movements in their head and neck, may be helped with the use of botulinum toxin more than placebo. A similar review found that botulinum toxin A may be slightly more helpful at decreasing symptoms of this condition compared to another type of medication called an anticholinergic that is also used to treat this condition.
- In people who have unwanted eyelid closure, a review done by Cochrane Systematic Reviews found that botulinum toxin is slightly more effective than placebo in reducing the severity of this condition.
- Botulinum toxin was studied for people that have chronic migraine headaches, which is 15 or more migraine headaches a month. The review found that the use of botulinum toxin decreased the number of headaches each month by about two, compared to placebo.
- A review and recommendation made by the National Institute for Health and Care Excellence recommends that botulinum toxin may be an option in people that have multiple sclerosis, who have muscle spasms, if the recommendation is made by a specialist and they have tried other medications such as baclofen and gabapentin.
- A new drug, daxibotulinum toxin A (DAXIFY), was approved for decreasing wrinkles. There are no studies to determine if it is better or worse than existing treatments.

Conditions treated with botulinum toxins that were not effective:

- Botulinum toxin was studied in children who walk on their toes for no known reason. There was only one study included in this review that found a small decrease in the amount of toe walking with the use of botulinum toxin A but recommended more studies to determine if there was a true benefit.
- A review done by the Canadian Agency for Drugs and Technologies in Health reviewed the use of botulinum toxin A to help reduce pelvic pain in women and did not find good information to support using it for this purpose.
- The Drug Use Research and Management Group recommends that no changes be made to the current policy that is in place for the use of botulinum toxin in patients that have fee-for-service medical coverage. Members that are under 21 years of age and have need for botulinum toxin for the use of decreasing excessive drooling, caused by another medical condition, should be evaluated on a case-by-case basis to see if botulinum toxin may be helpful.

**Research Questions:**

1. Is there new comparative evidence evaluating treatments or preventative therapies using BoNT based on relevant disease states/conditions?
2. Is there new comparative harms data for BoNT treatments (e.g., withdrawals due to adverse events, severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain BoNT treatments are more effective or cause less harm?

**Conclusions:**

- There were 11 new systematic reviews and meta-analyses, two new guidelines, seven randomized controlled trials, and one new drug covering nine different types of disease states reviewed in this drug class update. There were no studies which specifically studied Medicaid patients.

### Conditions in which literature supports the use of BoNT:

- A review by the Agency for Health Care Research and Quality (AHRQ) evaluated the use of botulinum neurotoxin type A (BoNT-A) for the use in urinary incontinence (UI) in women.<sup>1</sup> There was high-quality evidence that BoNT-A, compared to no treatment, demonstrated higher cure rates for urgency UI (odds ratio [OR] 4.9; 95% confidence interval [CI], 2.82 to 8.65).<sup>1</sup> There was high-quality evidence that in all types of UI BoNT-A was more effective than no treatment for cure rates (OR 5.67; 95 CI, 2.80 to 11.4).<sup>1</sup>
- There is high-quality evidence from a 2018 Canadian Agency for Drugs and Technologies in Health (CADTH) review that BoNT-A improves urgency symptoms, more than placebo, in people with overactive bladder (OAB).<sup>2</sup> There is low-quality evidence that BoNT-A reduces pain symptoms in people with bladder pain syndrome (BPS)/interstitial cystitis (IC).<sup>2</sup>
- A Cochrane Review found moderate-quality evidence of a small benefit, when compared to placebo, for the treatment of sialorrhea in adults with motor neuron disease (MND).<sup>3</sup> A reduction of 0.5 mL in saliva production in 5 minutes was demonstrated with botulinum neurotoxin type B (BoNT-B) compared to placebo at 8 weeks. The clinical significance of this is unknown. There was no evidence to support the use of BoNT-A for the treatment of sialorrhea.
- A review done by Cochrane evaluated BoNT-A use in children with cerebral palsy (CP) to treat lower limb spasticity. There is moderate-quality evidence that in the short term (follow-up 2 to 8 weeks) BoNT-A was more effective than placebo in improving gait scores (RR 1.66; 95% CI, 1.16 to 2.37; p=0.006; 4 randomized controlled trial [RCTs]).<sup>4</sup> Benefits were also seen in medium-term follow-up (12 to 18 weeks). Adverse events (AEs) were similar between groups.
- A Cochrane Systematic Review evaluating treatments for cervical dystonia (CD) in adults found moderate-quality evidence that BoNT-A was more effective at reducing symptoms of CD (based on Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] total score) at 4 weeks with a mean difference [MD] of 8.09 points higher with placebo (95% CI, 6.22 to 9.96).<sup>5</sup> This minimal clinically significant difference (MCID) is 12 points; therefore, this effect was not considered clinically significant. Other outcomes, including health related quality of life, were also improved with the use of BoNT-A compared to placebo.
- There is low-quality evidence from one trial in adult participants, reviewed by CADTH, that the use of incobotulinum toxin A is more effective than placebo for the treatment of sialorrhea associated with neurologic disorders based on salivary flow.<sup>6</sup>
- A Cochrane review found moderate quality evidence that a one-time BoNT-A injection is more effective than placebo in reducing the severity of blepharospasms.<sup>7</sup>
- There is high-quality evidence that the use of BoNT-A for the treatment of migraine is more effective than placebo for reducing the number of headache days per month, in adults with chronic migraine, by a mean decrease of 1.9 days (95% CI, -2.7 to -1.0; 2 RCTs) based on a review by Cochrane Database for Systematic Reviews.<sup>8</sup> There is insufficient evidence that the use of BoNT-A is effective for improving episodic migraine.
- The use of BoNT-A is recommended by National Institute for Health and Care Excellence (NICE) as an option for the management of overactive bladder (OAB) in women with urinary incontinence (UI) and pelvic prolapse who have not responded to pharmacotherapy.<sup>9</sup>
- New evidence from five RCTs support new indications for abobotulinum toxin A (e.g., upper limb spasticity in pediatric patients), onabotulinum toxin A (e.g., upper limb spasticity in pediatric patients, lower limb spasticity in pediatric patients, and pediatric neurogenic detrusor overactivity) rimabotulinum toxin B (e.g., chronic sialorrhea in adults) and incobotulinum toxin A (e.g., chronic sialorrhea in patients 2 years of age and older, upper limb spasticity in pediatric patients, chronic sialorrhea in adults).
- There is moderate-quality evidence that new agent, daxibotulinum toxin A (DAXIFY), is effective in improving glabellar lines (not covered by OHP) based on evidence from two trials.<sup>10</sup> There are no direct or indirect treatment comparisons to other BoNT-A therapies.

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#### Conditions treated with BoNT that lacked conclusive evidence of effectiveness:

- A 2019 review done by Cochrane found that there is very low-quality evidence that BoNT-A improved idiopathic toe walking (ITW) in children (relative risk [RR] 1.21; 95% CI, 0.57 to 2.55; p<0.05).<sup>11</sup>
- There is very low-quality evidence that BoNT-A reduces symptoms of CD in adults more than trihexyphenidyl based on a Cochrane Systematic Review.<sup>12</sup>
- A Rapid Response Review by CADTH found very low-quality evidence for the use of BoNT-A, compared to placebo, reduces symptoms of pelvic pain in women.<sup>13</sup>
- An evidence review from NICE found very low-quality evidence that BoNT-A was more effective than placebo for elucidating a positive response when used for spasticity in people with multiple sclerosis (MS).<sup>14</sup> The recommendation by NICE is that BoNT-A only be used by a specialist due to a lack of high-quality data.<sup>14</sup>

For most indications there was a lack of high-quality evidence for the use of botulinum toxin in children and adolescents. For UI there was insufficient evidence for the use of BoNT-A in a subgroup analysis of older women.

#### **Recommendations:**

- Update PA criteria to allow for coverage of BoNT products under the EPSDT program for persons under 21 years of age that is consistent with high-quality evidence.
- No changes to the preferred drug list (PDL) are recommended based on the review of the evidence.
- After evaluation of costs in executive session, no changes to the PDL are recommended.

#### **Summary of Prior Reviews and Current Policy:**

- Botulinum toxins used for migraines were reviewed in May of 2019 and at that time there were no changes to the PDL.
- The PA criteria for chemodenervation using botulinum toxin for the treatment of chronic migraine was updated in September 2018, to cover botulinum toxins for patients with migraine headache that have failed treatment with anticonvulsants, tricyclics and beta-blockers. Renewal of botulinum toxin therapy requires a 7 day or more reduction in headaches from baseline headache frequency. Treatment is limited to two injections given three months apart.
- A list of preferred treatment options is available in Appendix 2.
- Botulinum toxins are administered by a provider and are therefore classified as physician administered drugs (PADs). In the 4<sup>th</sup> quarter of 2022, there was a small number of claims for BoNT. All botulism products are listed in Appendix 1 and are required to go through prior authorization criteria to ensure use for an approved diagnosis.

#### **Background:**

Botulinum toxin works by blocking acetylcholine release at the neuromuscular junction, preventing muscular contraction.<sup>15</sup> Botulinum toxin is available in two serotypes, botulinum toxin type A and botulinum toxin type B. There are four Food and Drug Administration (FDA) approved BoNT-A products and one BoNT-B product currently available. The different botulinum toxin preparations are not interchangeable and potencies are specific for the different formulations. A list of approved BoNTs and their indications are listed in **Table 1**. Botulinum toxin lasts for three to six months dependent upon indication. **Table 2** describes requirements for BoNT coverage for OHP FFS patients as determined by the Health Evidence Review Commission (HERC) and outlined on the Prioritized List of Health Services.

**Table 1. FDA Approved Botulinum Products**

Generic Name	Brand Name	FDA Indication
Onabotulinum toxin A <sup>16</sup>	BOTOX BOTOX COSMETIC	<ul style="list-style-type: none"> <li>• Overactive bladder with symptoms of urge incontinence, urgency and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.</li> <li>• 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</li> <li>• Treatment of neurogenic detrusor overactivity in pediatric <b>patients 5 years</b> of age or older who have an inadequate response to or are intolerant of an anticholinergic medication</li> <li>• Prophylaxis of headache in adults with chronic migraine (15 or more days per month with headache lasting 4 hours a day or longer)</li> <li>• Treatment of spasticity in <b>patients 2 years</b> of age and older</li> <li>• Treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain</li> <li>• Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients</li> <li>• Treatment of blepharospasm associated with dystonia in <b>patients 12 years</b> of age and older</li> <li>• Treatment of strabismus in <b>patients 12 years of age and older</b></li> </ul>
Abobotulinum toxin A <sup>17</sup>	DYSPORT	<ul style="list-style-type: none"> <li>• Cervical dystonia in adults</li> <li>• Temporary improvement in the appearance of moderate to severe glabellar lines associated with the procerus and corrugator muscle activity in adults &lt; 65 years of age</li> <li>• Treatment of spasticity in <b>patients 2 years</b> of age and older</li> </ul>
Incobotulinum toxin A <sup>18</sup>	XEOMIN	<ul style="list-style-type: none"> <li>• Chronic sialorrhea in <b>patients 2 years</b> of age and older</li> <li>• Upper limb spasticity in adults</li> <li>• Upper limb spasticity in pediatric <b>patients 2 to 17</b> years of age, excluding spasticity caused by cerebral palsy</li> <li>• Cervical dystonia in adults</li> <li>• Blepharospasm in adults</li> <li>• Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults</li> </ul>
Prabotulinum toxin A <sup>19</sup>	JEUVEAU	<ul style="list-style-type: none"> <li>• Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients</li> </ul>
Rimabotulinum toxin B <sup>20</sup>	MYOBLOC	<ul style="list-style-type: none"> <li>• Cervical dystonia to reduce severity of abnormal head position and neck pain associated with cervical dystonia in adults</li> <li>• Chronic sialorrhea in adults</li> </ul>
Daxibotulinum toxin A <sup>10</sup>	DAXXIFY	<ul style="list-style-type: none"> <li>• Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.</li> </ul>

Clinical conditions that are treated with BoNTs include neuromuscular disorders (e.g., strabismus, blepharospasm, dystonia, spasticity), urinary disorders (e.g., neurogenic urologic disorders and symptoms of refractory urinary incontinence, urgency and/or frequency), sialorrhea and pain syndromes (e.g., migraine) (Table 2).<sup>21</sup> In addition to approved uses, BoNTs are commonly used off-label for many indications, some include: dystonia, ophthalmology indications, pelvic and bladder pain, otorhinolaryngology, and gastroparesis.

Adverse events reported with BoNT include respiratory, speech or swallowing difficulties that may lead to death. Botulinum toxins should be used cautiously in individuals that may have compromised respiratory function or dysphagia. There have been cardiovascular adverse events reported that may occur and potentially lead to death; therefore caution should be used in treating individuals with cardiovascular disease. An enhanced effect of BoNT may be seen in those with underlying neuromuscular disorders. Increased risk of urinary tract infections has been reported when BoNT is used for the treatment of OAB as well as urinary retention. There is a potential for bronchitis and upper respiratory infection when using BoNT for spasticity. All BoNT products have a boxed warning for the risk of spread from the area of injection to produce local and systemic symptoms of botulinum toxin effects. The symptoms have been seen hours to weeks after injection which may result in life threatening swallowing and breathing difficulties and even of death.<sup>16</sup> These AE are more likely to occur in children treated for muscle spasticity; however they can occur in adults and more likely if they have conditions that may predispose them to these AE.<sup>16</sup>

The main outcomes used to determine the efficacy and clinical impact of botulinum toxins are dependent upon the disease state being treated. Table 2 describes the different indications for which BoNT is used, as well as the most common outcome assessment metric and associated minimal clinically important difference if available. Table 2 also outlines requirements for BoNT coverage for OHP FFS patients as determined by the Health Evidence Review Commission (HERC) and outlined on the Prioritized List of Health Services.

**Table 2. Indications for Botulinum Therapy with Associated Outcomes and Coverage under the Oregon Health Plan**

Indication	Outcome Assessment	Prioritized List of Health Services Coverage*
Cervical Dystonia <sup>12,22</sup> <ul style="list-style-type: none"> <li>• Movement disorder characterized by disabling, painful muscle contractions of the neck</li> <li>• BoNT-A is recommended as a first-line treatment</li> </ul>	Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) <ul style="list-style-type: none"> <li>• Range 0-85, higher is worse</li> <li>• 12 point change is considered the MCID<sup>23</sup></li> </ul> Tsui Scale <ul style="list-style-type: none"> <li>• 6 item scale accessing involuntary neck movement</li> <li>• Scores range from 1-25</li> <li>• MCID not determined</li> </ul>	Line 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD10-CM G24.9).
Spasticity <sup>24</sup> <ul style="list-style-type: none"> <li>• Abnormal increase in muscle tone or stiffness</li> <li>• Standard therapy is occupational and/or</li> </ul>	Ashworth Scale <ul style="list-style-type: none"> <li>• Scale ranges from 0-4 (4 is more rigid)</li> <li>• MCID is a change of 1 point or more</li> </ul>	Line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS Chemodenervation with botulinum toxin injection (CPT 64642-64647) is included on this line for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83)

<p>physiotherapy with antispasticity pharmacotherapy</p>	<p>Global Impression of Change Scale (GICS)</p> <ul style="list-style-type: none"> <li>scale ranges from -3 to +3 (higher is better)</li> </ul>	
<p>Overactive bladder<sup>25</sup> (Neurogenic detrusor overactivity / Urinary incontinence)</p> <ul style="list-style-type: none"> <li>Associated with urgency, frequency and with or without incontinence</li> <li>First-line therapy recommendations include antimuscarinics</li> </ul>	<p>Overactive bladder symptom score (OABSS)</p> <ul style="list-style-type: none"> <li>Scores range from 0-15, with higher scores indicating more symptoms</li> <li>A decrease of 3 points is the MCID</li> </ul>	<p>Line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic or beta-3 adrenergic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium, mirabegron, vibegron). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction on of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.</p>
<p>Sialorrhea<sup>6</sup></p> <ul style="list-style-type: none"> <li>Excessive drooling often due to a neurologic disorder</li> </ul>	<p>There are no validated outcome measures with MCIDs</p>	<p>Not covered – falls below line 472. Line 500 SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS Chemodenervation with botulinum toxin injection (CPT 64611) is included on this line for the treatment of excessive salivation. (ICD-10 -CM K11.5-K11.9,R68.2)</p>
<p>Blepharospasm<sup>7</sup></p> <ul style="list-style-type: none"> <li>Focal dystonia characterized by involuntary eyelid closure</li> <li>Botulinum toxin is considered first-line therapy</li> </ul>	<p>Jankovic Rating Scale (JRS) severity subscore</p> <ul style="list-style-type: none"> <li>Values of 0-4 with lower values being better</li> <li>MCID not determined</li> </ul> <p>Patient Evaluation of Global Response (PEGR)</p> <ul style="list-style-type: none"> <li>Values of -4 to +4 with higher scores suggesting benefit</li> <li>MCID not determined</li> </ul>	<p>Line 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD10-CM G24.9).</p>
<p>Strabismus</p> <ul style="list-style-type: none"> <li>Misalignment of the eye</li> </ul>	<p>Correction of eye alignment</p>	<p>Line 351 STRABISMUS DUE TO NEUROLOGIC DISORDER Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10-CM H50.89).</p>

<ul style="list-style-type: none"> <li>Managed with corrective lenses, eye exercises, surgery or botulinum injection</li> </ul>		
Migraine Headaches <sup>26</sup> <ul style="list-style-type: none"> <li>Moderate to severe headache attacks</li> <li>First-line treatment options include: beta-blockers, anticonvulsants and tricyclic antidepressants</li> <li>Botulinum is indicated for chronic migraine headaches</li> </ul>	Migraine frequency Migraine Disability Assessment Score (MIDAS) <ul style="list-style-type: none"> <li>Scores of 0-5 are indicative of little or no disability, 6-10 mild disability, 11-20 moderate disability, and 21 or greater as severe disability.</li> <li>MCID is 4.5 points</li> </ul>	Line 410 MIGRAINE HEADACHES Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria: A) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine B) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (e.g. beta-blocker, anticonvulsant or tricyclic antidepressant) C) their condition has been appropriately managed for medication overuse D) treatment is administered in consultation with a neurologist or headache specialist. Treatment is limited to two injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.
Reduction in moderate to severe glabellar lines	Improved appearance	Not a covered indication.
Esophageal stricture <ul style="list-style-type: none"> <li>Trouble swallowing</li> <li>Narrowing of the esophagus</li> </ul>	Not FDA approved for this indication	Covered by OHP: Line 378 ESOPHAGEAL STRICTURE; ACHALASIA Chemodenervation with botulinum toxin injection (CPT 43201) is included on this line for treatment of achalasia (ICD-10 K22.0).
Abbreviations: BoNT-A = botulinum toxin A; FDA = Food and Drug Administration; MCID = minimal clinically important difference; NA = not applicable; OHP = Oregon Health Plan. Key: * As determined by the Health Evidence Review Commission (HERC) Guideline Notes for February 1, 2023 Prioritized List of Health Services.		

Additional botulinum toxin indications not covered by the HERC Prioritized List due to lack of evidence:

- Guideline Note 37, surgical interventions for conditions of the back and spine other than scoliosis
- Guideline Note 145, treatments for benign prostate enlargement with lower urinary tract symptoms
- Line 517 disorders of sweat glands, chemodenervation with botulinum toxin injection (CPT 64650, 64653) is included on this line for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10-CM L74.52, R61).
- Line 526 chronic anal fissure, chemodenervation with botulinum toxin injection (CPT 46505) is included on this line for the treatment of anal fissures.

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence

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(NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **New Systematic Reviews:**

#### AHRQ – Nonsurgical Treatments for Urinary Incontinence in Women

In 2018 AHRQ updated 2012 guidance for the treatment of UI in women.<sup>1</sup> A total of 233 studies were included. Community-dwelling women who were not pregnant with symptoms of UI were included in the eligible population. Study participants were women between the ages of 33 and 85 years old (median age of 55 years).<sup>1</sup> Nonpharmacological, pharmacological and combination therapies were included in the analysis. Pharmacological treatment options included the following: anticholinergics, BoNT-A, hormones (e.g., estrogens), alpha agonists, beta agonists, antidepressants, and periurethral bulking agents. The main outcomes of interest were cure (or complete resolution) of UI symptoms (incontinence, urgency and frequency). For the purpose of this review the use of BoNT-A for UI will be presented.

Onabotulinum toxin A is considered a third-line treatment for UI. Two studies evaluated BoNT-A for urgency UI and reported cure rates. BoNT-A was found to be more effective than no treatment (OR 4.9; 95% CI, 2.82 to 8.65) (high-quality evidence).<sup>1</sup> Evaluation of all types of UI (two studies) found BoNT-A to be superior to no treatment for cure rates (OR 5.67; 95% CI, 2.80 to 11.4) (high-quality evidence). There was low quality evidence that BoNT-A had similar efficacy cure rates as neuromodulation for all types of incontinence and urgency UI, RR 1.69 (95% CI, 0.80 to 3.62) and RR 1.68 (95% CI, 0.80 to 3.55) ( $P \geq 0.80$  for both).<sup>1</sup> Evidence summary of efficacy found BoNT-A to be associated with a 43.6% cure rate in women with urgency UI. There was insufficient evidence for the use of BoNT-A in a subgroup analysis of older women (>65 years). Overall, the risk of bias was considered low across all the studies.

In women with urgency UI, indirect evidence found BoNT-A to be more effective than no treatment (OR 3.6; 95% CI, 1.8 to 7.3) based on high-quality evidence.<sup>1</sup> There were no direct comparisons of third line treatment options. The overall percent of women who found improvement with BoNT-A for urgency UI was 66.6%.<sup>1</sup> Low strength of evidence found BoNT-A to be more effective than neuromodulation for achievement of patient satisfaction in women with UI (OR 1.3; 95% CI, 0.93 to 2.1).<sup>1</sup> Overall, 85.5% of women were satisfied with BoNT-A when used for urgency UI.<sup>1</sup>

Thirty-eight percent of women experienced a treatment related AE when treated with BoNT-A for UI. Urinary tract infections (UTI) were the most common AE which occurred in 35% of women receiving BoNT-A (moderate-quality of evidence).<sup>1</sup> There was moderate-quality of evidence that BoNT-A was associated with urinary retention or voiding dysfunction in 18% of women.<sup>1</sup>

Limitations to this systematic review include: the inclusion of direct and indirect evidence, small number of trials available for analysis, small sample size and lack of evidence in subgroup populations, such as women over the age of 65 years.

### CADTH – Intravesical Botulinum Toxin for Adults with Non-Neurogenic Bladder Conditions

A CADTH rapid response clinical effectiveness review evaluated BoNT-A for the treatment of non-neurogenic bladder conditions (e.g. OAB, idiopathic detrusor activity, and bladder pain).<sup>2</sup> Literature was searched till February 2019, which identified four systematic reviews, three RCTs and four guidelines. Participants in the studies were adults with a diagnosis of OAB or BPS/IC.

There was high quality evidence that BoNT-A 100 units, compared to placebo or compared to anticholinergics (e.g., solifenacin, oxybutynin, fesoterodine, trospium, darifenacin, tolterodine) improved urgency episodes associated with OAB.<sup>2</sup> Botulinum toxin A (100 to 500 U) reduced pelvic pain in people with BPS/IC compared to placebo based on high quality evidence. Guidelines recommend BoNT-A as a third-line agent, after pharmacotherapy, for OAB based on moderate to high quality evidence. Guidelines recommend BoNT-A for the treatment of BPS/IC for people who are refractory to other treatments (weak strength of evidence).<sup>2</sup> Adverse events of BoNT-A were an increased incidence of urinary tract infections (UTIs) and urinary retention compared to placebo.

### Treatment for Sialorrhea (excessive saliva) in People with Motor Neuron Disease/Amyotrophic Lateral Sclerosis

A 2022 Cochrane Review evaluated the use of BoNT A and B in people with sialorrhea as a result of MND (e.g., ALS).<sup>3</sup> Other treatments studied were dextromethorphan hydrobromide, quinidine sulfate and scopolamine; however only results for botulinum toxins will be presented. Four trials (n=110) in patients with MND were included. Participants were 21-85 years of age. Studies were considered to be at low risk of bias.

Normal daily salivary production ranges from 0.5 liters (L) to 1.0 L.<sup>3</sup> The use of BoNT-B was compared to placebo in one small study of 20 people. At eight weeks BoNT-B was found to decrease salivary production by -0.50 mL/5 min (95% CI, -1.07 to 0.07) (moderate quality evidence).<sup>3</sup> Patient reported improvements in sialorrhea symptoms when treated with BoNT-B compared to placebo but results were not statistically significant and based on very low quality of evidence. There was low quality of evidence that BoNT-B may improve quality of life compared to placebo based on the Schedule for Evaluation of Individual Quality of Life direct weighting scale. Adverse events were similar between BoNT-B and placebo, based on low quality of evidence.

A pilot study in 20 people evaluating BoNT-A compared to placebo provided very low quality evidence that there was not a clinical benefit with active treatment.<sup>3</sup>

Limitations to the evidence are lack of large, high-quality trials with objectively measured outcomes. Authors concluded that the evidence was too uncertain to drawn firm conclusions on the role of BoNT-A for sialorrhea.

### Cochrane – Interventions for Idiopathic Toe Walking

In 2019 Cochrane reviewed the evidence for the use of interventions in children with ITW.<sup>11</sup> Only one study was included that involved 46 participants who had an average age of 5.1 years. Botulinum toxin was injected bilaterally at a dose of 12 U/kg body weight. The main outcome was improvement in toe walking, defined as parent-reported toe walking less than 50% of the time.

The use of BoNT-A with conservative treatment (e.g., casting below the knee for four weeks) was more effective than conservative treatment alone based on one trial with very low quality evidence (RR 1.21; 95% CI, 0.57 to 2.55; follow-up at 12 months).<sup>11</sup> This benefit was not demonstrated with the use of BoNT-A passive ankle joint dorsiflexion range of movement on the right with the knee extended, on the right with the knee flexed or on the left with the knee extended. There was no demonstrated benefit of BoNT-A on recurrence of toe-walking gait (MD 0.34; 95% CI, -0.09 to 0.78) based on very low quality evidence.<sup>11</sup> There was very low quality evidence that there was no treatment discontinuations due to treatment.

The evidence was based on an open-label study design and therefore subject to a high risk of bias. There is insufficient evidence to support the use of BoNT-A for ITW in children.

#### Cochrane – Botulinum Toxin Type A in the Treatment of Lower Limb Spasticity in Children with Cerebral Palsy

Cochrane Systematic Reviews evaluated the use of BoNT-A for children who are diagnosed with CP and have lower limb spasticity.<sup>4</sup> Botulinum toxin A was compared to usual care/physiotherapy, placebo or sham treatment, serial casting, or orthoses (external devices). Children were birth to 19 years of age, the mean age was three to seven years old and a majority were males.<sup>4</sup> Most participants had more than one motor type of CP. Thirty-one trials (n=1508) were included. The primary outcome was gait analysis and function measured at 3 time points: short-term follow-up (2 to 8 weeks), medium term follow-up (12 to 16 weeks) and long term follow-up (>24 weeks).

Authors rated the studies as having a high or unclear risk of bias mostly due to blinding concerns introducing performance and detection bias.<sup>4</sup> Comparisons of BoNT-A to usual care/physiotherapy were based on very low quality evidence. Function scores at 2 to 8 weeks were found to be more improved with the use of BoNT-A compared to usual care/physiotherapy (SD 0.59; 95% CI, 0.23 to 0.95; 2 RTCs), which is considered a moderate effect to treatment.<sup>4</sup> Range of motion was found to be slightly improved with BoNT-A compared to usual care/physiotherapy; however, the difference was small and there was high heterogeneity across trials. Spasticity was found to be similar between groups with the use of BoNT-A compared to usual care/physiotherapy (SD 1.19; 95% CI, 2.62 to 0.24).<sup>4</sup> Adverse events were higher in those treated with BoNT-A with 0.37 proportion in the BoNT-A group experiencing an event.

Efficacy comparisons between BoNT-A and usual care/physiotherapy done at a follow-up of 12 to 16 weeks were based on very low-quality evidence. Observational gait score was higher in the BoNT-A group (MD 2.80; 95% CI, 1.55 to 4.05; 1 RCT).<sup>4</sup> Function was improved with BoNT-A compared to usual care/physiotherapy (SD 1.04; 95% CI, 0.16 to 1.91) based on four studies and was associated with high heterogeneity. The difference was considered to be a large effect. Botulinum toxin A was associated with more improvement in range of motion (6.36 degrees; 95% CI, 4.03 to 8.69; passive ankle dorsal flexion; 5 trials).<sup>4</sup> Spasticity was lower in participants treated with BoNT-A compared to usual care/physiotherapy by a decrease in symptoms of a standard mean difference of 1.66 (95% CI, 2.88 to 0.43; 3 RCTs), which was considered a large effect.<sup>4</sup>

Short term (follow-up 2 to 8 weeks) found BoNT-A to be more effective than placebo or sham in improving gait scores based on moderate quality evidence (RR 1.66; 95% CI, 1.16 to 2.37; p=0.006; 4 RCTs).<sup>4</sup> Gait improvements were also seen at medium-term follow-up (12 to 18 weeks) in participants receiving BoNT-A compared to placebo or sham (RR 1.90; 95% CI, 1.32 to 2.74; P<0.001; 3 RCTs).<sup>4</sup> Short-term follow up demonstrated improvements in peak ankle dorsiflexion in stance and swing, based on moderate evidence, mean difference 15.90 (95% CI, 4.87 to 26.93; p=0.005) and mean difference 10.20 (95% CI, 4.01 to 16.39; p=0.001), respectively.<sup>4</sup> Function scores were not improved with BoNT-A compared to sham or placebo in the short or long term; however a small effect was demonstrated in the medium term (SMD 0.28; 95% CI, 0.06 to 0.49; P=0.01; 5 RCTs) (moderate quality evidence).<sup>4</sup> Adverse events were similar between groups at short-term follow up visits (moderate strength of evidence).

There was no difference between the use of BoNT-A and serial casting for short, medium, long-term follow up for most outcomes based on one RCT (moderate quality of evidence). Instrumental gait analysis (ankle dorsiflexion at initial contact) was improved with BoNT-A compared to serial casting (MD 6.59 degrees; 95% CI, 1.39 to 11.78; P=0.01; 2 RCTs) (moderate quality of evidence).<sup>4</sup> Low quality evidence found no difference in incidence of adverse events.

Very low quality evidence found BoNT-A was more effective than orthoses at improving hip range of motion and hip adductors spasticity; however function was not improved at medium term follow up.<sup>4</sup>

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All trials included in the analysis were small and of limited duration. The quality of evidence was determined to be very low quality for many outcomes and additional high-quality studies are needed.

#### Cochrane – Botulinum Toxin Type A for Cervical Dystonia

Cochrane performed a systematic review and evidence evaluation for the treatments for CD in adult patients.<sup>5</sup> Nine RCTs (n=1144) comparing a single BoNT-A treatment to placebo were included in the review. The mean age was 52.8 years and 64% were female. Duration of CD ranged from 4.8 years to 12.1 years and severity of CD was moderate to severe (TWSTRS score of 13.9 to 14.4). Types of BoNT-A included: 150 units to 500 units onabotulinum toxin A (BOTOX), 120 units to 240 U of incobotulinum toxin A (XEOMIN), and 250 units to 1000 units abobotulinum toxin A (DYSPORT).<sup>5</sup> The primary outcome of interest was CD improvement as assessed by TWSTRS score (range 0-85, higher values equated with worse symptoms). Outcomes were assessed at 4-6 weeks.

The authors determined the overall risk of bias to be moderate for the included studies. BoNT-A was more effective at reducing symptoms of CD (based on TWSTRS total score) at 4 weeks with a MD of 8.09 points higher with placebo (95% CI, 6.22 to 9.96) (moderate quality evidence).<sup>5</sup> Subjective participant assessment of symptoms was much improved in those treated with BoNT-A compared to placebo (RR 2.19; 95% CI, 1.78 to 2.70), based on high-quality evidence. Pain due to CD was lower in those treated with BoNT-A with a MD of 2.11 points increase in those treated with placebo (based on TWSTRS pain scale, 0-20 with higher scores worse) (moderate quality evidence). There were a higher number of dropouts in those treated with BoNT-A compared to placebo, based on high quality evidence (RR 0.48; 95% CI, 0.32 to 0.73).<sup>5</sup> Health related quality of life was higher in participants treated with BoNT-A compared to placebo, based on moderate quality evidence). There was moderate quality evidence that AEs were higher in those treated with BoNT-A (RR 1.23; 95% CI, 1.05 to 1.43).<sup>5</sup>

Limitations included the exclusion of patients with a previous poor response to BoNT-A in participating in seven of the nine studies.

#### Cochrane – Botulinum Toxin Type A versus Anticholinergics for Cervical Dystonia

Cochrane updated a 2005 review in 2021 on the management of CD with BoNT-A, which is considered first-line treatment.<sup>12</sup> Trials comparing BoNT-A to anticholinergics were included. Only one trial was identified, which included 66 adult participants with an average age of 50.7 years. The severity of CD was moderate, average TWSTRS score of 15.9. Two doses of BoNT-A, abobotulinum toxin A 262 units (week 8) and 292 units (week 0) were compared to trihexyphenidyl, up to 24 mg daily.<sup>12</sup> All participants were BoNT-A naïve. The primary outcome was measurement of CD symptoms by the TWSTRS.

The trial was rated as having moderate risk of bias due to multiple domains that had uncertain risk of bias. At 12 weeks, BoNT-A reduced CD severity by 2.5 points (95% CI, 0.68 to 4.32) compared to trihexyphenidyl (very low quality evidence).<sup>12</sup> There were 31 adverse events in the BoNT-A group compared to 76 events in those treated with trihexyphenidyl. There was less dry mouth and memory problems in those treated with BoNT-A compared to trihexyphenidyl. Additional studies are needed to determine the comparative efficacy of BoNT-A to anticholinergics.

#### CADTH – Injectable Botulinum Toxin for Pelvic Pain

Botulinum toxin for use in women with pelvic pain was evaluated by CADTH in a 2019 rapid response review.<sup>13</sup> A literature search up to July of 2019 identified three RCTs and two systematic reviews to provide evidence for the use of BoNT-A for pelvic pain (BoNT-B was not studied). Adult patients, 18 years and older, with pelvic floor pain due to vulvodynia, vaginismus, endometriosis and short pelvic floor syndrome were included. Bladder conditions were excluded. Patients included in the systematic reviews were a mean age of 26 years and those in the RCTs ranged from a median of 27 to 42 years.<sup>13</sup>

Findings from one of the systematic reviews found transvaginal BoNT-A (50-300 U) effective for dyspareunia with a decrease of 2.3-4.47 points in the 10-point visual analog scale (VAS) compared to placebo, which is higher than the MCID (low quality evidence; cohort studies).<sup>13</sup> Patients with vestibulodynia did not show benefit with BoNT-A treatment. A second systematic review found no difference between BoNT-A and placebo for vaginismus, including BoNT-A injections, behavioral sex therapy, cognitive behavioral therapy (CBT), pharmacological therapy, pelvic floor physiotherapy, and removal of hymenal remnants.

A RCT found that BoNT-A was not more effective in decreasing muscle pain compared to placebo.<sup>13</sup> A small study found no difference between BoNT-A 50 U, BoNT-A 100 U and placebo in pain, based on VAS, at three months. A third, small (n=58) RCT found physiotherapy was more effective than BoNT-A for improvements in sexual function.<sup>13</sup> Additional, high-quality evidence is needed to support the use of BoNT-A for pelvic pain.

Limitations to the evidence include limited external validity with the enrollment of specific groups of participants (e.g., highly educated, failed other treatments and those with severe pain). Many outcomes were self-reported by patients and may be prone to recall bias.

#### CADTH – Incobotulinum toxin A Reimbursement Review

The Canadian Agency for Drugs and Technology in Health reviewed the use of incobotulinum toxin A for the treatment of moderate to severe chronic sialorrhea associated with neurologic disorders.<sup>6</sup> Recommendations for use were based on a review of one clinical trial (n=184) comparing incobotulinum toxin A 100 U to placebo in adult patients that demonstrated reduction in salivary flow with the use of incobotulinum toxin A (SIAXI<sup>27</sup>; trial details available in **Table 3**).

After review of the evidence, CADTH recommends that incobotulinum toxin A should be an option for the treatment of moderate to severe chronic sialorrhea associated with neurologic disorders if the following criteria are met:<sup>6</sup>

- In the care of a specialist with experience in managing neurologic conditions
- Sialorrhea lasting for at least 3 months or more
- Drooling severity and frequency scale (DSFS) sum score of 6 or greater and frequency and severity score of 2 or more
- No evidence of dysphagia
- Initial authorization of 16 weeks (dose of 100 units at interval of at least 16 weeks or longer is recommended)
- Renewals are recommended for those people who have a reduction in frequency and/or severity of sialorrhea

#### Cochrane – Botulinum Toxin Type A Therapy for Blepharospasms

The efficacy of BoNT-A in the management of blepharospasms was the focus of a 2020 Cochrane systematic review.<sup>7</sup> Three RCTs were identified enrolling a total of 313 participants with a mean age of 61.2 years and 66% female. All studies evaluated a one-time treatment of BoNT-A at 4 to 6 weeks after injection.<sup>7</sup> Studies enrolled people with moderate to severe blepharospasm impairment. The primary outcome was symptom improvement using validated measurements (e.g., JRS severity subscore).

The trials were considered to be at low to moderate risk of overall bias. Botulinum toxin A was compared to placebo and was found to reduce blepharospasm-specific severity (measured by the JRS severity scale) by a mean difference of 0.93 (95% CI, 0.61 to 1.25) based on moderate strength of evidence.<sup>7</sup> Subjective participant evaluation (measured by the Patient Evaluation of Global Response [PEGR]) was higher (more effective) in those treated with BoNT-A compared to placebo (SMD 0.86; 95% CI, 0.53 to 1.2) based on high quality evidence. Low quality evidence from two RCTs found BoNT-A to be more effective at reducing the frequency of blepharospasm-specific involuntary movements when compared to placebo (SMD 0.79; 95% CI, 0.31 to 1.27). One trial found the duration of BoNT-

A to last an average of 10.6 weeks (moderate quality of evidence). Adverse events were similar with BoNT-A compared to placebo (RR 1.18; 95% CI, 0.87 to 1.60) (low quality of evidence).<sup>7</sup>

Limitations include two of the trials excluding individuals with a prior history of poor response to BoNT-A, selecting out responders to therapy.

#### Cochrane – Botulinum toxins for the Prevention of Migraine

A 2018 Cochrane Systematic Review evaluated the evidence for the use of BoNT-A in adult patients with chronic or episodic migraine in adults.<sup>8</sup> Twenty-eight studies were included, with 4190 participants. The mean age was 42 years old and 85% were women. Eleven trials allowed Concomitant prophylactic medications at stable doses. Migraine severity ranged from mild to severe. The main outcomes were number of migraine days a month and global disease impact. The global disease impact was measured by the Migraine Impact and Disability Assessment Score (MIDAS).

The overall quality of evidence was considered very low all trials (episodic and chronic).<sup>8</sup> Only one trial evaluated the use of BoNT for episodic migraine and found no difference between BoNT-A and placebo ( $p=0.49$ ) for the number of migraine days per month.<sup>8</sup>

The use of BoNT-A was compared to placebo in 23 trials as a preventative treatment for chronic migraine. There was high quality evidence that the use of BoNT-A reduced the number of headache days per month in those with chronic migraine by a mean decrease of 1.9 days (95% CI, 2.7 to 1.0 lower).<sup>8</sup> The number of migraine days per month in those with chronic migraine was also decreased with BoNT-A compared to placebo (MD 3.1; 95% CI, 4.7 to 1.4) (low quality evidence). Adverse events were higher in participants treated with BoNT-A compared to placebo based on moderate quality of evidence (RR 1.28; 1.12 to 1.47; 13 RCTs).<sup>8</sup>

In a comparison of BoNT-A to prophylactic therapy for migraine prevention (e.g., topiramate) found very low-quality evidence that there was no difference between groups for the number of migraine days per month in those with chronic migraine. The use of BoNT-A did result in one less headache day per month compared to topiramate (MD 1 day; 95% CI, -4.3 to 2.3 days;  $p>0.05$ ); however, the results are not statistically significant.<sup>8</sup> The MIDAS score was 4.3 points higher (95% CI, -28 to 37) in those treated with BoNT-A compared to topiramate (very low quality evidence).<sup>11</sup>

The quality of evidence was low to very low for many outcomes, thus limiting conclusions on overall effectiveness for BoNT-A in chronic migraine. There is a need for more high-quality trials comparing BoNT-A to other chronic migraine preventative therapies to adequately determine the place in therapy for BoNT-A in treating migraine.

After review, 12 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).<sup>28–35,36–39</sup>

#### **New Guidelines:**

##### High Quality Guidelines:

##### NICE – Urinary Incontinence and Pelvic Organ Prolapse in Women

Guidance on the treatment of UI and pelvic organ prolapse in adult women was updated in 2019.<sup>9</sup> NICE recommends nonsurgical management and oral medication for treating overactive bladder, which is often the cause of incontinence. Invasive procedures can be offered to people who continue to have symptoms despite nonsurgical management or treatment with medications. In people with detrusor overactivity, leading to OAB symptoms, NICE recommends

bladder wall injection with BoNT-A if the patients has not responded to non-surgical measures, including pharmacotherapy.<sup>9</sup> In women with OAB that is not caused by detrusor overactivity and symptoms have not responded to non-surgical management BoNT-A is recommended as an option. All women should be advised that the use of BoNT-A may result in increased risk of UTIs and need for intermittent catheterization due to voiding dysfunction. There is insufficient evidence on the long-term use of BoNT-A for UI.

Initial dosing of BoNT-A for overactive bladder is 100 units.<sup>9</sup> If additional doses are required, 200 units of BoNT-A 12 weeks later can be used. It is recommended that if symptoms improved initially but were not sustained until 6 months with a 100 units of BoNT-A, a dose of 200 units should be offered at 12 weeks. The use of botulinum toxin B is not recommended for OAB.

### NICE – Multiple Sclerosis in Adults: Management

In June of 2022 NICE conducted an evidence review on the pharmacological management of spasticity in people with MS that included evidence from three RCTs comparing botulinum to placebo.<sup>14</sup> Included patients were 18 years of age or older. Participants were allowed to take stable antispasticity medications and analgesic medications. Patients had baseline Modified Ashworth Scores (MAS) of 8.5 to 16, Expanded Disability Status Scale (EDSS) scores greater than 7 and history of having MS for 12.9 to 22.9 years.<sup>14</sup> Trials were small with 74-106 participants in each and outcomes were measured at 4 and 8 weeks. Important outcomes were: spasticity scales (e.g., MAS, Tardieu Scale, Muscle Elastography MS Scale [MEMSs], Fugl Meyer Scale [FMS]), patient reported measures of spasticity (e.g., Penn Spasm Frequency Scale, Numeric Rating Scale for Spasticity (NRS-S), MS Spasticity Scale-88 [MSSS], Patient Reported Impact of Spasticity Measure [Prism]), functional scales (e.g., EDSS), health related quality of life and adverse events. Outcomes were categorized as three to six months follow-up or greater than six month follow up.

All studies were downgraded due to serious concerns with imprecision. All efficacy outcomes were based on very low quality of evidence.<sup>14</sup> A positive response (e.g., MAS, muscle tone and clinical global rating) was higher in those treated with BoNT-A 500, 1000 or 1500 units compared to placebo. Those treated with BoNT-A 500 units demonstrated a positive response in 61.9% of participants compared to 43.8% treated with placebo (RR 1.41; 95% CI, 0.74 to 2.71).<sup>14</sup> Positive response rates were higher for participants treated with 1000 units BoNT-A compared to placebo (RR 1.09; 95% CI, 0.53 to 2.22) and for those treated with 1500 units (RR 1.08; 95% CI, 0.51 to 2.28).<sup>14</sup> There was moderate quality of evidence that BoNT-A was associated with more adverse events compared to placebo (RR 3.71; 95% CI, 1.11 to 12.39). NICE recommends that BoNT-A should only be used if recommended by a specialist due to the lack of clinical evidence.

After review, three guidelines were excluded due to poor quality.<sup>40-42</sup>

### **New Formulations or Indications:**

#### Abobotulinum toxin A (DYSPORT):

- In September of 2019, abobotulinum toxin A was approved for the treatment of upper limb spasticity in pediatric patients 2 years of age and older, excluding spasticity caused by cerebral palsy.<sup>17</sup> Details and results of the trial used for approval are outlined in **Table 3**.

#### Onabotulinum toxin A (BOTOX):

- In June of 2019, onabotulinum toxin A received an indication for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age.<sup>16</sup> Approval was based on one unpublished, multi-center, double-blind, placebo-controlled RCT of pediatric patients with upper limb spasticity due to

CP or stroke randomized to onabotulinum toxin A 3 units/kg, 6 units/kg or placebo.<sup>16</sup> The primary endpoint was MAS and the Clinical Global Impression of Overall Change by Physician (CGI), the average of week 4 and 6 for both outcomes. The mean change from baseline in MAS was -1.92, -1.87 and -1.21 for onabotulinum toxin A 3 units/kg, onabotulinum toxin A 6 units/kg and placebo, respectively ( $p < 0.05$  compared to placebo for both groups).<sup>16</sup> The change in CGI was 1.88, 1.87 and 1.66 for onabotulinum toxin A 3 units/kg, onabotulinum toxin A 6 units/kg and placebo, respectively ( $p > 0.05$  for all comparisons).

- Onabotulinum toxin A was approved for use for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age.<sup>16</sup> One multi-center, double-blind, placebo-controlled RCT demonstrated the efficacy of onabotulinum toxin A in pediatric patients with CP. The primary endpoint was MAS and the CGI, average of week 4 and 6 for both outcomes. Onabotulinum toxin A 4 units/kg decreased MAS by -1.01 ( $p < 0.05$ ), onabotulinum toxin A 8 units/kg by -1.06 and placebo by -0.80. The CGI changed by 1.49, 1.65 and 1.36 for onabotulinum toxin A 4 units/kg, 8 units/kg and placebo, respectively.
- In February 2021 onabotulinum toxin A was approved for the treatment of pediatric neurogenic detrusor overactivity. Details and results of the trial used for approval are outlined in **Table 3**.<sup>43</sup>
- In July of 2021 onabotulinum toxin A was approved for 8 additional upper limb muscles within the approved muscle groups for the adult upper limb spasticity indication.<sup>16</sup>

#### Rimabotulinum toxin B (MYOBLOC):

- Rimabotulinum toxin B received a new indication for the treatment of chronic sialorrhea in adults in August of 2019.<sup>20</sup> Approval was based off of two studies that were phase 3, double-blind, placebo-controlled RCTS. The first trial studied adult patients with sialorrhea for at least 3 months associated with Parkinson's disease, ALS, stroke or other causes. The co-primary outcomes were unstimulated salivary flow rate USFR and Clinical Global Impression of Change (CGI-C) at week four. A single treatment of rimabotulinum 2,500 units reduced the USFR by -0.37 gram (g)/minute (min), rimabotulinum 3,500 units decreased USFR by -0.36 g/min and placebo decreased USFR by -0.07 g/min.<sup>20</sup> Both doses of rimabotulinum were statistically superior to placebo. The CGI-C was 2.38 for rimabotulinum of 2,500 units, 2.45 for rimabotulinum of 3,500 units and 3.59 for placebo ( $p < 0.001$  for both doses compared to placebo). The second study was conducted in mostly male, adult patients with Parkinson's disease. At week four, rimabotulinum 1,500 units decreased USFR by -0.44, rimabotulinum 2,500 units decreased USFR by -0.38 ( $p < 0.001$ ) and rimabotulinum 3,500 units decreased USFR by -0.30 ( $p < 0.001$ ) and placebo increased USFR by 0.01 g/min.<sup>20</sup> CGI-C scores were improved in those participants treated with rimabotulinum 1,500 units, rimabotulinum of 2,500 units and rimabotulinum 3,500 units compared to placebo, 2.14 ( $p < 0.0001$ ), 2.00 ( $p < 0.0001$ ), 1.62 ( $p < 0.0001$ ) and 3.93, respectively.<sup>20</sup>

#### Incobotulinum toxin A (XEOMIN)

- Incobotulinum toxin A was approved in for the treatment of chronic sialorrhea in patients 2 years of age and older in December of 2020.<sup>18</sup> Approval was based on a double-blind, placebo-controlled trial of patients 6-17 years, patients 2-5 years received open-label treatment. Results were based on patients 6-17 years of age. At week 4, incobotulinum toxin A was more effective than placebo for changes in uSFR and GICS ( $p < 0.05$ ).<sup>18</sup>
- In August of 2020 incobotulinum toxin A was approved for treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy. Incobotulinum toxin A was studied in a double-blind, placebo-controlled trial in pediatric patients with upper limb spasticity. At week 4 the changes in AWS were more effective for incobotulinum toxin A 8 units/kg compared to 2 units/kg, which served as the control ( $p < 0.05$ ). Changes in the other co-primary outcome, GICS, was not statistically different between groups.<sup>18</sup>
- Incobotulinum received an additional indication in July 2018 for the treatment of chronic sialorrhea in adults.<sup>18</sup> Details and results of the trial used for approval are outlined in **Table 3**.<sup>27</sup>

DaxibotulinumtoxinA-ianm (DAXXIFY)

- DaxibotulinumtoxinA-ianm was approved in by the FDA on September 7, 2022 for adult patients for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity. Daxibotulinum toxin A is give as 8 units into five sites for a total dose of 40 units.<sup>10</sup> Evidence used for approval are outlined in **Table 3**. Common adverse reactions are headache, eyelid ptosis, and facial paresis. Like other BoNT products, daxibotulinum has a boxed warning for the risk of spread with the potential to cause swallowing and breathing difficulties which can be life threatening and there have been reports of death. Daxibotulinum toxin is not indicated for the treatment of spasticity.<sup>10</sup>

**New FDA Safety Alerts:**

No new safety alerts identified.

**Randomized Controlled Trials:**

A total of 88 citations were manually reviewed from the initial literature search. After further review, 82 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining seven trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

**Table 3. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Austin, et al <sup>43</sup>  DB, MC, Phase 3, RCT	Onabotulinum toxin A 50 units as one dose  Onabotulinum toxin A 100 units as one dose  Onabotulinum toxin A 200 units as one dose	Children ages 5 to 17 years with NDO and UI	Change from baseline in daytime UI episodes at week 6	Onabotulinum toxin A 50 units: -1.3 episodes/day Onabotulinum toxin A 100 units: -1.3 episodes/day Onabotulinum toxin A 200 units: -1.3 episodes/day	The 50 unit dose was used due to ethical concerns of placebo use in children for this indication.  <i>Onabotulinum toxin was considered to be effective for the treatment of NDO in pediatrics.</i>
Carruthers, et al <sup>44</sup>  SAKURA 1  DB, MC, Phase 3, RCT	Daxibotulinum toxin A 40 units as one dose  Placebo	Patients with moderate to severe glabellar lines as measured by the Investigator Global Assessment -	2 or more point improvement in glabellar line severity (as measured by the GAFWAS and PFWS) at maximum frown at week 4	Daxibotulinum toxin A: 298 (73.6%) Placebo: 0% P<0.0001	<i>Daxibotulinum toxin A was more effective than placebo in reducing glabellar lines.</i>

		Frown Wrinkle Assessment Scale (GAFWAS) and the Patient Frown Wrinkle Scale (PFWS)			
Carruthers, et al <sup>44</sup>  SAKURA 2  DB, MC, Phase 3, RCT	Daxibotulinum toxin A 40 units as one dose  Placebo	Patients with moderate to severe glabellar lines	2 or more point improvement in glabellar line severity at maximum frown at week 4	Daxibotulinum toxin A: 151 (74.0%) Placebo: 2 (1.0%) P<0.0001	<i>Daxibotulinum toxin A was more effective than placebo in reducing glabellar lines.</i>
Dabrowski, et al <sup>45</sup>  DB, MC, Phase 3, RCT	Incobotulinum toxin A 8 units/kg (max dose 200 units/upper limb)  Incobotulinum toxin A 6 units/kg (max dose 150 units/upper limb)  Incobotulinum toxin A 2 units/kg (control group) (max dose 50 U/upper limb)  - Patients had option of entering open-label extension trial. - Stable centrally acting antispastic medication was allowed - Patients could receive unilateral or bilateral lower-limb injections in addition	Children ages 2 to 17 years with unilateral or bilateral spastic CP and Ashworth Scale* (AS) score of 2 or greater  (n=372)	Change from baseline at week 4 in the AS score for the main clinical target pattern chosen from flexed elbow or wrist. Co-primary outcome was the investigator's Global Impression of Change Scale+ (GICS) for the upper limb	AS Score: Incobotulinum toxin A 8 units/kg: -1.15 Incobotulinum toxin A 6 units/kg: -1.02 Incobotulinum toxin A 2 units/kg: -0.93  <u>Incobotulinum toxin A 8 units/kg vs. Incobotulinum toxin A 2 units/kg:</u> TD -0.22; P=0.017 (No CI provided)  <u>Incobotulinum toxin A 6 units/kg vs. Incobotulinum toxin A 2 units/kg:</u> TD -0.09; P=0.546 (No CI provided)  <u>Investigator's GICS score:</u> Incobotulinum toxin A 8 units/kg: 1.64 Incobotulinum toxin A 6 units/kg: 1.44 Incobotulinum toxin A 2 units/kg: 1.55	Difference between groups is considered clinically significant. There was no difference between the doses for the outcome of GICS.  Limitations to the study was that there was no placebo-controlled group, small sample size and short study duration.  <i>Greater spasticity improvements were seen in patients treated with incobotulinum toxin A 8 units/kg compared to 2 units/kg.</i>

	to upper limb injections			P = >0.05 for all comparisons	
Delgado, et al <sup>46</sup>  DB, MC, Phase 3, RCT	<p>Abobotulinum toxin A 16 units/kg (maximal total body dose of 640 units)</p> <p>Abobotulinum toxin A 8 units/kg (maximal total body dose of 320 units)</p> <p>Abobotulinum toxin A 2 units/kg (control) (maximal total body dose of 80 U)</p> <p>- All patients also received personalized, goal-oriented home exercise therapy program (HETP)</p>	<p>Children ages 2 to 17 years with CP and Modified Ashworth Score (MAS) of 2 or greater and Gross Motor Function Classification System (GMFCS) of I to IV.</p> <p>(n=210)</p>	Change from baseline in MAS at week 6 of cycle 1	<p>Abobotulinum toxin A 16 units/kg: -2.3</p> <p>Abobotulinum toxin A 8 units/kg: -2.0</p> <p>Abobotulinum toxin A 2 units/kg: -1.6</p> <p><u>Abobotulinum toxin A 16 units/kg vs. Abobotulinum toxin A 2 units/kg:</u> TD -0.7; P&lt;0.001 (No CI provided)</p> <p><u>Abobotulinum toxin A 8 units/kg vs. Abobotulinum toxin A 2 units/kg:</u> TD -0.4; P=0.012 (No CI provided)</p>	<i>Abobotulinum toxin A 8 units/mg and 18 units/kg was effective in treating spasticity associated with CP that was clinically significant.</i>
Heinen F, et al <sup>47</sup>  DB, MC, Phase 3, RCT	<p>Incobotulinum toxin A 4 units/kg (max dose 100 units)</p> <p>Incobotulinum toxin A 12 units/kg (max dose 300 units)</p> <p>Incobotulinum toxin A 16 units/kg (control group) (max dose 400 units)</p>	<p>Children (2-17 years) with lower-limb unilateral or bilateral CP related spasticity and AS plantar flexor (PF) score of 2 or greater</p> <p>(n=311)</p>	Change from baseline in AS-PF score at 4 weeks and co-primary outcome was the investigator's Global Impression of Change Scale+ (GICS)	<p>AS-PF Score:</p> <p>Incobotulinum toxin A 4 units/kg: -0.68</p> <p>Incobotulinum toxin A 12 units/kg: -0.69</p> <p>Incobotulinum toxin A 16 units/kg: -0.70</p> <p>P&lt;0.0001 for all comparison to baseline values</p> <p><u>GICS-PF score:</u></p> <p>Incobotulinum toxin A 4 units/kg: 1.5</p>	<i>Use of incobotulinum toxin A did not result in a clinically significant benefit in lower-limb spasticity despite results being statistically significant.</i>

				<p>Incobotulinum toxin A 12 units/kg: 1.51</p> <p>Incobotulinum toxin A 16 units/kg: 1.54</p> <p>P&lt;0.0001 for all comparisons to baseline values</p>	
<p>Jost W, et al<sup>27</sup></p> <p>DB, MC, PC, Phase 3, RCT</p>	<p>Incobotulinum toxin A 75 units as a single dose</p> <p>Incobotulinum toxin A 100 units as a single dose</p> <p>Placebo</p>	<p>Adult patients with chronic sialorrhea due to Parkinson's disease, atypical Parkinsonism, stroke or traumatic brain injury</p> <p>(n=184)</p>	<p>Co-primary endpoint of uSFR from baseline and GICS at week 4</p>	<p>Change in USF at 4 weeks:</p> <p>Incobotulinum toxin A 75 units: -0.06</p> <p>Incobotulinum toxin A 100 units: -0.13</p> <p>Placebo: -0.04</p> <p><u>Incobotulinum toxin A 75 units vs. placebo:</u></p> <p>LS mean -0.02 (No CI provided)</p> <p>P=0.542</p> <p><u>Incobotulinum toxin A 100 units vs. placebo:</u></p> <p>LS mean -0.09 (No CI provided)</p> <p>P=0.004</p> <p><u>Changes in GICS at 4 weeks:</u></p> <p>Incobotulinum toxin A 75 units: 1.05</p> <p>Incobotulinum toxin A 100 units: 1.28</p> <p>Placebo: 0.7</p> <p><u>Incobotulinum toxin A 75 units vs. placebo:</u></p> <p>LS mean 0.35 (No CI provided)</p> <p>P=0.055</p> <p><u>Incobotulinum toxin A 100 units vs. placebo:</u></p> <p>LS mean 0.58 (No CI provided)</p> <p>P=0.002</p>	<p><i>Incobotulinum toxin 100 units was effective in reducing the uSFR more than placebo; however, it is unknown if the decrease is clinically significant.</i></p>

Key: \*Ashworth Scale = five point scale from 0 (no increase in muscle tone) to 4 (limb rigidity in flexion/extension); + Global Impression of Change Scale = seven-point Likert scale from -3 (very much worse) to +3 (very much improved) for the impression of change in spasticity compared to the condition before the last injection.

Abbreviations: AS = Ashworth scale CI = confidence interval; CP = cerebral palsy; DB = double-blind; GICS= Global Impression of Change Scale; kg = kilogram; LS = least squares; MAS = Modified Ashworth Score; MC = multi-center; NDO = neurogenic detrusor overactivity; PF = plantar flexor; RCT = randomized clinical trial; TD = treatment difference; U = units; UI = urinary incontinence; uSFR = unstimulated salivary flow rate.

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## Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>
abobotulinumtoxinA	DYSPORE	VIAL
incobotulinumtoxinA	XEOMIN	VIAL
onabotulinumtoxinA	BOTOX	VIAL
onabotulinumtoxinA	BOTOX COSMETIC	VIAL
prabotulinumtoxinA-xvfs	JEUVEAU	VIAL
rimabotulinumtoxinB	MYOBLOC	VIAL
daxibotulinumtoxinA-lanm	DAXXIFY	VIAL

## Appendix 2: Abstracts of Comparative Clinical Trials

### IncobotulinumtoxinA Efficacy/Safety in Upper-Limb Spasticity in Pediatric Cerebral Palsy: Randomized Controlled Trial

Edward Dabrowski , Marta Banach, Petr Kaňovský, Hanna Dersch, Michael Althaus , Thorin L Geister, Florian Heinen

**Background:** This randomized phase 3 study with double-blind main period (MP) and open-label extension (OLEX; NCT02002884) assessed incobotulinumtoxinA safety and efficacy for pediatric upper-limb spasticity treatment in ambulant/nonambulant (Gross Motor Function Classification System [GMFCS] I-V) patients, with the option of combined upper- and lower-limb treatment.

**Methods:** Patients were aged two to 17 years with unilateral or bilateral spastic cerebral palsy (CP) and Ashworth Scale (AS) score  $\geq 2$  in treatment-selected clinical patterns. In the MP, patients were randomized (2:1:1) to incobotulinumtoxinA 8, 6, or 2 U/kg body weight (maximum 200, 150, 50 U/upper limb), with optional lower-limb injections in one of five topographical distributions (total body dose  $\leq 16$  to 20 U/kg, maximum 400 to 500 U, depending on body weight and GMFCS level). In the OLEX, patients received three further treatment cycles, at the highest MP doses (8 U/kg/upper limb group). Outcomes included AS, Global Impression of Change Scale (GICS), and adverse events (AEs).

**Results:** AS scores improved from baseline to week 4 in all MP dose groups (n = 350); patients in the incobotulinumtoxinA 8 U/kg group had significantly greater spasticity improvements versus the 2 U/kg group (least-squares mean [standard error] for upper-limb main clinical target pattern -1.15 [0.06] versus -0.93 [0.08]; P = 0.017). Investigator's, child/adolescent's, and parent/caregiver's GICS scores showed improvements in all groups. Treatment benefits were sustained over further treatment cycles. AE incidence did not increase with dose or repeated treatment across GMFCS levels.

**Conclusions:** Data provide evidence for sustained efficacy and safety of multipattern incobotulinumtoxinA treatment in children and adolescents with upper-limb spasticity.

### Efficacy and safety of abobotulinumtoxinA for upper limb spasticity in children with cerebral palsy: a randomized repeat-treatment study

Mauricio R Delgado, Ann Tilton, Jorge Carranza-Del Río, Nigar Dursun, Marcin Bonikowski, Resa Aydin, Iwona Maciag-Tymecka, Joyce Oleszek, Edward Dabrowski, Anne-Sophie Grandoulier, Philippe Picaut; Dysport in PUL study group

**Aim:** To assess the efficacy and safety of repeat abobotulinumtoxinA injections in reducing upper limb spasticity in children with cerebral palsy (CP).

**Method:** This was a double-blind, repeat-cycle study (NCT02106351) in children with CP (2-17y). Children were randomized to receive 2U/kg (control), 8U/kg, or 16U/kg abobotulinumtoxinA injections into the target muscle group (wrist or elbow flexors) and additional muscles alongside occupational therapy via a home-exercise therapy program (HETP; minimum five 15min sessions/wk). Children received 8U/kg or 16U/kg plus HETP in cycles 2 to 4.

**Results:** During cycle 1, 210 children (126 males, 84 females; mean age [SD] 9y [4y 5mo], range 2-17y; n=70/group) had at least one upper limb abobotulinumtoxinA injection and 209 complied with the HETP. At week 6 of cycle 1, children in the 8U/kg or 16U/kg groups had significantly lower Modified Ashworth scale scores versus the 2U/kg group (primary outcome: treatment differences of -0.4 [p=0.012] and -0.7 [p<0.001] respectively). All groups improved on Physician Global Assessment and children in all groups achieved their treatment goals at least as expected. Therapeutic benefits were sustained during cycles 2 to 4; muscular weakness was the only treatment-related adverse event reported in at least one child/group (4.3% and 5.7% vs 1.4% respectively).

**Interpretation:** Treatment with 8U/kg or 16U/kg abobotulinumtoxinA significantly reduced upper limb spasticity versus the 2U/kg control dose. Therapeutic benefits of abobotulinumtoxinA plus HETP were sustained with repeat treatment cycles.

### **Long-term Safety and Tolerability of Repeated Treatments With OnabotulinumtoxinA in Children With Neurogenic Detrusor Overactivity**

Israel Franco, Piet B Hoebeke, Eric Dobremez, Wilson Titanji, Till Geib, Brenda Jenkins, Irina Yushmanova, Paul F Austin

**Purpose:** OnabotulinumtoxinA is an approved treatment for neurogenic detrusor overactivity in adults inadequately managed with anticholinergics, and more recently was approved in children on the basis of a phase 3, 48-week, single-treatment study (NCT01852045). Given the paucity of long-term pediatric data, we report on the continued safety in these patients after repeated onabotulinumtoxinA treatment.

**Materials and methods:** This was a multicenter, double-blind, repeat-treatment extension study (NCT01852058) in patients who entered from the preceding single-treatment study. Data were integrated across both studies. All patients (5-17 years) used clean intermittent catheterization and could receive dose escalations based on response to preceding treatment (50 U, 100 U, or 200 U onabotulinumtoxinA [not to exceed 6 U/kg]).

**Results:** Overall, 95, 90, 55, and 11 patients received 1, 2, 3, and 4 treatments with onabotulinumtoxinA, respectively, and median (quartiles) duration of follow-up was 82 (65, 94) weeks. The safety profile was similar across doses and after repeat treatments. The most common treatment-emergent adverse event during cycles 1, 2, and 3 was urinary tract infection (31%, 34%, 22%). Three serious treatment-emergent adverse events related to study treatment (3/95; 3.2%) were reported during the study, which were all cases of urinary tract infection. Annualized urinary tract infection rates post-treatment were similar to pre-screening rates. There were no cases of autonomic dysreflexia, neutralizing antibodies, and treatment-emergent adverse events related to distant spread of toxin.

**Conclusions:** OnabotulinumtoxinA continued to be well tolerated after repeated treatments in pediatric neurogenic detrusor overactivity patients with similar safety profiles across dose groups. Treatment-emergent adverse events were primarily urological with no new safety concerns.

### **OnabotulinumtoxinA for the treatment of neurogenic detrusor overactivity in children**

Paul F Austin, Israel Franco, Eric Dobremez, Pawel Kroll, Wilson Titanji, Till Geib, Brenda Jenkins, Piet B Hoebeke

**Aims:** This study evaluated whether one (or more) of three doses of onabotulinumtoxinA were safe and effective to treat neurogenic detrusor overactivity (NDO) in children.

**Methods:** This was a 48-week prospective, multicenter, randomized, double-blind study in children (aged 5-17 years) with NDO and urinary incontinence (UI) receiving one onabotulinumtoxinA treatment (50, 100, or 200 U; not to exceed 6 U/kg). Primary endpoint: change from baseline in daytime UI episodes.

Secondary endpoints: change from baseline in urine volume at first morning catheterization, urodynamic measures, and positive response on the treatment benefit scale. Safety was also assessed.

**Results:** There was a similar reduction in urinary incontinence from baseline to Week 6 for all doses (-1.3 episodes/day). Most patients reported positive responses on the treatment benefit scale (75.0%-80.5%). From baseline to Week 6, increases were observed in urine volume at first morning clean intermittent catheterization (50 U, 21.9 ml; 100 U, 34.9 ml; 200 U, 87.5 ml; p = 0.0055, 200 U vs. 50 U) and in maximum cystometric capacity (range 48.6-63.6 ml) and decreases in maximum detrusor pressure during the storage phase (50 U, -12.9; 100 U, -20.1; 200 U, -27.3 cmH<sub>2</sub> O; p = 0.0157, 200 U vs. 50 U). The proportion of patients experiencing involuntary detrusor contractions dropped from baseline (50 U, 94.4%; 100 U, 88.1%; 200 U, 92.6%) to Week 6 (50 U, 61.8%; 100 U, 44.7%; 200 U, 46.4%). Safety was similar across doses; urinary tract infection was most frequent.

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**Conclusions:** OnabotulinumtoxinA was well tolerated and effective for the treatment of NDO in children; 200 U showed greater efficacy in reducing bladder pressure and increasing bladder capacity.

**IncobotulinumtoxinA for the treatment of lower-limb spasticity in children and adolescents with cerebral palsy: A phase 3 study**

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**Purpose:** Investigate the efficacy and safety of multipattern incobotulinumtoxinA injections in children/adolescents with lower-limb cerebral palsy (CP)-related spasticity.

**Methods:** Phase 3 double-blind study in children/adolescents (Gross Motor Function Classification System - Expanded and Revised I-V) with unilateral or bilateral spastic CP and Ashworth Scale (AS) plantar flexor (PF) scores  $\geq 2$  randomized (1:1:2) to incobotulinumtoxinA (4, 12, 16 U/kg, maximum 100, 300, 400 U, respectively) for two 12- to 36-week injection cycles. Two clinical patterns were treated. Pes equinus (bilateral or unilateral) was mandatory; if unilateral, treatment included flexed knee or adducted thigh.

**Endpoints:** Primary: AS-PF change from baseline to 4 weeks; Coprimary: investigator-rated Global Impression of Change Scale (GICS)-PF at 4 weeks; Secondary: investigator's, patient's, and parent's/caregiver's GICS, Gross Motor Function Measure-66 (GMFM-66).

**Results:** Among 311 patients, AS-PF and AS scores in all treated clinical patterns improved from baseline to 4-weeks post-injection and cumulatively across injection cycles. GICS-PF and GICS scores confirmed global spasticity improvements. GMFM-66 scores indicated better motor function. No significant differences between doses were evident. Treatment was well-tolerated, with no unexpected treatment-related adverse events or neutralising antibody development.

**Conclusion:** Children/adolescents with lower-limb spasticity experienced multipattern benefits from incobotulinumtoxinA, which was safe and well-tolerated in doses up to 16 U/kg, maximum 400 U.

### Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 22, 2023

Search Strategy:

#	Searches	Results
1	abobotulinumtoxinA.mp.	495
2	incobotulinumtoxinA.mp.	494
3	onabotulinumtoxinA.mp.	1282
4	prabotulinumtoxinA.mp.	23
5	rimabotulinumtoxinB.mp.	628
6	1 or 2 or 3 or 4 or 5	2531
7	limit 6 to (english language and humans and yr="2018 -Current")	709
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	87

### Appendix 4: Key Inclusion Criteria

<b>Population</b>	Patients with indications for botulinum toxin
<b>Intervention</b>	Botulinum toxin A and botulinum toxin B
<b>Comparator</b>	Placebo or active treatment
<b>Outcomes</b>	Dependent upon indication being treated (see Table 2)
<b>Timing</b>	Not applicable
<b>Setting</b>	Outpatient

## Botulinum Toxins

### Goal(s):

- Approve use of botulinum toxins for conditions funded under the Oregon Health Plan (OHP) and supported by evidence of benefit.
- Require positive response to therapy for continued use to manage chronic migraine headaches or overactive bladder.
- Allow case-by-case review for members covered under the EPSDT program.

### Length of Authorization:

- From 90 days to 12 months

### Requires PA:

- Use of botulinum toxins (billed as a physician administered or pharmacy claim) without associated dystonia or neurological disease diagnosis in last 12 months.

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor muscle over-activity (“overactive bladder”)?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #2
2. What diagnosis is being treated?	Record ICD10 code	

## Approval Criteria

<p>3. Is botulinum toxin treatment for any of the following?</p> <ol style="list-style-type: none"> <li>Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83)</li> <li>Strabismus due to a neurological disorder (H50.89)</li> <li>Blepharospasm (G24.5)</li> <li>Spasmodic torticollis (G24.3)</li> <li>Torsion dystonia (G24.9)</li> <li>Achalasia (K22.0)</li> </ol>	<p><b>Yes:</b> Approve for up to 12 months</p>	<p><b>No:</b> Go to #4</p>
<p>4. Is botulinum toxin treatment for chronic migraine, with <math>\geq 15</math> headache days per month, of which <math>\geq 8</math> days are with migraine?</p>	<p><b>Yes:</b> Go to #5 Baseline headaches per month: _____</p>	<p><b>No:</b> Go to #8</p>
<p>5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?</p>	<p><b>Yes:</b> Go to #6</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
<p>6. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs (in the same or different drug classes)?</p> <ul style="list-style-type: none"> <li>Propranolol immediate-release, metoprolol, or atenolol</li> <li>Topiramate, valproic acid, or divalproex sodium</li> <li>Amitriptyline, nortriptyline, or venlafaxine</li> </ul>	<p><b>Yes:</b> Go to #7</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at <a href="http://www.orpdl.org/drugs/">www.orpdl.org/drugs/</a></p>
<p>7. Do chart notes indicate headaches are due to medication overuse?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</p>	<p><b>No:</b> Approve no more than 2 injections given <math>\geq 3</math> months apart within a 12 month time period.</p> <p>Additional treatment requires <u>documented</u> positive response to therapy from baseline (see Renewal Criteria).</p>

<b>Approval Criteria</b>		
8. Is botulinum toxin treatment detrusor muscle over-activity (“overactive bladder”)?	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Go to #10
9. Has the patient had an inadequate response to, or is intolerant to at least two urinary incontinence antimuscarinic or beta-3 adrenergic therapies, such as those listed below? a. Fesoterodine (OHP preferred) b. Oxybutynin (OHP preferred) c. Solifenacin (OHP preferred) d. Darifenacin e. Flavoxate f. Mirabegron g. Tolterodine h. Trospium i. Vibegron	<b>Yes:</b> <ul style="list-style-type: none"> <li>• Baseline urine frequency/day: _____.</li> <li>• Baseline urine incontinence episodes/day: _____.</li> </ul> <p>Approve for up to 90 days.</p> <p>Additional treatment requires <u>documented</u> positive response to therapy from baseline (see Renewal Criteria).</p>	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

10. Review treating condition, age, and ICD-10 code. ICD-10 codes included in the tables below are denied. If ICD-10 code is not included in the tables below, medical literature with evidence for use in funded conditions must be submitted by the prescriber. RPh may approve for up to 12 months for funded conditions with evidence of benefit.

**If current age  $\geq$ 21 years: Deny for the following conditions; not funded by the OHP**

**If current age <21 years, evaluate FDA-approved indications and disease severity. If the drug is FDA approved for the condition AND prescriber submits documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.), RPh may approve for up to 12 months.**

- Axillary hyperhidrosis and palmar hyperhidrosis (L74.52, R61)
- Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259)
- Facial nerve disorders (G510-G519)
- Spastic dysphonia (J387)
- Anal fissure (K602)
- Disorders of sweat glands (e.g., focal hyperhidrosis) (L301; L740-L759; R61)
- Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788)
- Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549)
- Disorders of soft tissue (M5410; M609; M790-M792; M797)
- Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51)
- Gastroparesis (K3184)
- Lateral epicondylitis (tennis elbow) (M7710-M7712)
- Unspecified diseases of the salivary glands (sialorrhea) (K11.5-K11.9,R68.2)

**Deny for medical appropriateness because evidence of benefit is insufficient**

- Dysphagia (R130; R1310-R1319)
- Other extrapyramidal disease and abnormal movement disorders (G10; G230-GG238; G2401; G244; G250-G26)
- Other disorders of binocular eye movements (e.g., esotropia, exotropia, mechanical strabismus, etc.) (H4900-H518)
- Tics (F950-F952; F959)
- Laryngeal spasm (J385)
- Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (M4802; M5412-M5413)
- Spasm of muscle in absence of neurological diagnoses (M6240-M62838)
- Contracture of tendon (sheath) in absence of neurological diagnoses (M6240; M62838)
- Amyotrophic sclerosis (G1221)
- Clinically significant spinal deformity or disorders of spine with neurological impairment (M4800; M4804; M4806; M4808; M5414-M5417)
- Essential tremor (G25.0)
- Hemifacial spasm (G513)
- Occupational dystonia (e.g., “Writer’s cramp”) (G248, G249)
- Hyperplasia of the prostate (N400-403; N4283)
- Conditions of the back and spine for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions. See Guideline Note 37.

Renewal Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	<b>Yes:</b> Go to #2	<b>No:</b> Go to #3
2. Is there documentation of a reduction of $\geq 7$ migraine headache days per month compared to baseline migraine headache frequency?	<b>Yes:</b> Approve no more than 2 injections given $\geq 3$ months apart.  Baseline:____ migraine headaches/month Current:____ migraine headaches/month	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of detrusor muscle over-activity (“overactive bladder”)?	<b>Yes:</b> Go to #4	<b>No:</b> Go to Approval Criteria
4. Is there a reduction of urinary frequency of $\geq 8$ episodes per day or urinary incontinence of $\geq 2$ episodes per day compared to baseline frequency?	<b>Yes:</b> Approve for up to 12 months  <ul style="list-style-type: none"> <li>• Baseline:____ urine frequency/day</li> <li>• Current:____ urine frequency/day</li> </ul> -or- <ul style="list-style-type: none"> <li>• Baseline:____ urine incontinence episodes/day</li> <li>• Current:____ urine incontinence episodes/day</li> </ul>	<b>No:</b> Pass to RPh. Deny; medical appropriateness

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