Clinical Policy Title:	incobotulinumtoxinA
Policy Number:	RxA.312
Drug(s) Applied:	Xeomin®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

IncobotulinumtoxinA (Xeomin®) is an acetylcholine release inhibitor and a neuromuscular blocking agent. Xeomin® is indicated for the treatment or improvement of:

- Chronic sialorrhea in patients 2 years of age and older;
- Upper limb spasticity in adults;
- Upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy;
- Cervical dystonia (CD) in adults;
- Blepharospasm in adults;
- Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

Dosing Information

<table>
<tr><th>Drug Name</th><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>incobotulinumtoxinA (Xeomin®)</td><td>Chronic sialorrhea</td><td>Xeomin® is injected into the parotid and submandibular glands on both sides (i.e., 4 injection sites per treatment session). The dose is divided with a ratio of 3:2 between the parotid and submandibular glands, no sooner than every 16 weeks
Adult:
<table><tr><th>Gland(s)</th><th>Unit per side</th><th>Total</th></tr><tr><td>Parotid gland(s)</td><td>30 units</td><td>60 units</td></tr><tr><td>Submandibular gland(s)</td><td>20 units</td><td>40 units</td></tr><tr><td>Both glands</td><td>50 units</td><td>100 units</td></tr></table>Pediatric:
<table><tr><th>Body weight</th><th>Parotid gland, each side</th><th>Submandibular gland, each side</th><th>Total dose, both glands,</th></tr></table></td><td>Adults: Max 100 units per treatment session
Pediatric: 75 units</td></tr>
</table>

Dosing Information

<table>
<tr><th>Drug Name</th><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td colspan="2"></td><td colspan="2"></td><td>both sides</td></tr>
<tr><td></td><td>Dose per gland</td><td>Volume per injection</td><td>Dose per gland</td><td>Volume per injection</td><td></td></tr>
<tr><td>12 kg < 15 kg</td><td>6 units</td><td>0.24 mL</td><td>4 units</td><td>0.16 mL</td><td>20 units</td></tr>
<tr><td>15 kg < 19 kg</td><td>9 units</td><td>0.36 mL</td><td>6 units</td><td>0.24 mL</td><td>30 units</td></tr>
<tr><td>19 kg < 23 kg</td><td>12 units</td><td>0.48 mL</td><td>8 units</td><td>0.32 mL</td><td>40 units</td></tr>
<tr><td>23 kg < 27 kg</td><td>15 units</td><td>0.6 mL</td><td>10 units</td><td>0.4 mL</td><td>50 units</td></tr>
<tr><td>27 kg < 30 kg</td><td>18 units</td><td>0.72 mL</td><td>12 units</td><td>0.48 mL</td><td>60 units</td></tr>
<tr><td>≥ 30 kg</td><td>22.5 units</td><td>0.9 mL</td><td>15 units</td><td>0.6 mL</td><td>75 units</td></tr>
</table>
</td><td></td></tr>
<tr><td></td><td>Cervical Dystonia</td><td>The usual starting dose is 120 units per treatment session, doses up to 400 units may be used in treatment- experienced patients. Dose, number, and location of injection sites should be based on the number and location of muscles involved, severity of dystonia, and response to any previous botulinum toxin injections. Administer no more frequently than every 3 months</td><td>120 units per treatment session</td></tr>
<tr><td></td><td>Blepharospasm</td><td>The recommended starting dose is 25 units per eye no more frequently than every 3 months</td><td>50 units per eye per treatment session</td></tr>
<tr><td></td><td>Upper limb spasticity</td><td>Dosing varies based on location of muscles to be treated (refer to dosing chart in the prescribing information).
Adults: the recommended total dose is up to 400 Units, divided among affected muscles
Pediatric Patients, excluding spasticity caused by cerebral palsy: the recommended total dose is 8 Units/kg (maximum 200 Units) per single upper limb or 16 Units/kg (maximum 400 U) in both upper limbs, divided among affected muscles. Administer no more frequently than every 3 months</td><td>400 units per treatment session</td></tr>
<tr><td></td><td>Glabellar Lines</td><td>4 units/injection IM with 2 injections in each corrugator muscle and 1 injection in the procerus muscle. Do not administer more frequently than every 3 months.</td><td>20 units per treatment session</td></tr>
</table>

Dosage Forms

- Injection: 50 Units, 100 Units, or 200 Units lyophilized powder in a single-dose vial.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Chronic Sialorrhea (must meet all)**:**

1. Diagnosis of chronic sialorrhea for at least the last three months due to an underlying neurologic disorder or craniofacial abnormality *(see Appendix D);*
2. Prescribed by or in consultation with a neurologist, physiatrist, or physical medicine and rehabilitation specialist;
3. Age ≥ 2 years;
4. Provider submits treatment plan detailing the quantity (in units) of Xeomin® to be injected in each gland, anticipated frequency of injection(s), and total dose per visit;
5. Dose does not exceed one of the following (a or b)
   a. For Adults: 100 units per treatment session;
   b. For Pediatric: 75 units per treatment session.

Approval duration:
Commercial: 6 months
Medicaid: 112 days (single treatment session)

B. Cervical Dystonia (must meet all)**:**

1. Diagnosis of CD (see Appendix E);
2. Prescribed by or in consultation with a neurologist, orthopedist, physiatrist, or physical medicine and rehabilitation specialist;
3. Age ≥ 18 years;
4. Experiencing involuntary contractions of the neck and shoulder muscles (e.g., splenius, sternocleidomastoid, levator scapulae, scalene, trapezius, semispinalis capitis) resulting in abnormal postures or movements of the neck, shoulder or head;
5. Contractions are causing pain and functional impairment;
6. Provider submits treatment plan detailing the quantity (in units) of Xeomin® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
7. Dose does not exceed 120 units per treatment session.

Approval duration:
Commercial: 6 months
Medicaid: 84 days (single treatment session)

C. Blepharospasm (a focal dystonia) (must meet all)**:**

1. Diagnosis of blepharospasm (i.e., abnormal contraction of eyelid muscles);
2. Prescribed by or in consultation with a neurologist or ophthalmologist;
3. Age ≥ 18 years;
4. Member has significant disability in daily functional activities due to interference with vision;
5. Provider submits treatment plan detailing the quantity (in units) of Xeomin® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
6. Dose does not exceed 50 units per eye per treatment session.

Approval duration:
Commercial: 6 months

Medicaid: 84 days (single treatment session)

D. Upper Limb Spasticity (must meet all)**:**

1. Diagnosis of upper limb spasticity;
2. Prescribed by or in consultation with a neurologist, orthopedist, physiatrist, or physical medicine and rehabilitation specialist;
3. Member meets one of the following (a or b);
   a. Age 2 to 17 years of age excluding spasticity caused by cerebral palsy;
   b. Age ≥ 18 years;
4. Provider submits treatment plan detailing the quantity (in units) of Xeomin® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. Dose does not exceed 400 units per treatment session.

Approval duration:
Commercial: 6 months
Medicaid: 84 days (single treatment session)

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. It has been at least 12 weeks (16 weeks if sialorrhea) since the last injection of Xeomin®;
4. Provider submits treatment plan detailing the quantity (in units) of Xeomin® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. If request is for a dose increase, new dose does not exceed the following indication specific maximums (a, b, c or d):
   a. Chronic sialorrhea (i or ii):
      i. Adult: 100 units per treatment session;
      ii. Pediatric: 75 units per treatment session.
   b. CD: 120 units per treatment session;
   c. Upper limb spasticity: 400 units per treatment session;
   d. Blepharospasm: 50 units per eye per treatment session.

Approval duration:
Commercial: 12 months
Medicaid: 84 days, or 112 days if sialorrhea (single treatment session)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CD: Cervical dystonia
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Botox® (onabotulinumtoxinA)	Cervical dystonia: Average Duration of Effect: 4 weeks to 3	400 units

	months Average Dose: 198 to 300 units (mean, 236 units) divided among affected muscles	
	<u>Blepharospasm:</u> Average duration of effect:12.5 weeks Initial Dose: 1.25 to 2.5 units into each of 3 sites per affected eye; Average Dose: 5 units per site	200 units total in a 30- day period
	<u>Upper limb spasticity:</u> Adult: Average duration of effect: 12 weeks Average dose: 12.5 units to 50 units in one site Pediatric: Average duration of effect: 12 weeks average dose: 3 units/kg to 6 units/kg divided among the affected muscles	Adult: 400 units Pediatric: 6 units/kg or 200 units, whichever is lower
Botox cosmetic	<u>Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients:</u> 20 units total dose divided equally (4 units/injection) and injected intramuscularly at 5 sites, 2 injections in each corrugator muscle and 1 injection in the procerus muscle	400 units per 3 month period

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to the active substance botulinum neurotoxin type A or to any of the excipients;
  - Infection at the proposed injection sites.

- Boxed warning(s):
  - Distant spread of toxin effect.

APPENDIX D: General Information

Examples of Neurologic Disorders and Craniofacial Abnormalities

- Neurologic Disorder:
  - Parkinson disease, atypical parkinsonism, stroke, traumatic brain injury, cerebral palsy, amyotrophic lateral sclerosis.
- Craniofacial abnormalities:
  - Goldenhar syndrome.

APPENDIX E: Definition *and Classification of Dystonia*

- Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
  - Dystonic movements are typically patterned, twisting, and may be tremulous.
  - Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.
- Dystonia is classified along two axes:
  - Clinical characteristics: Age at onset, body distribution, temporal pattern, associated features (additional movement disorders or neurological features) - *the clinical characteristics fall into several specific dystonia syndromes that help to guide diagnosis and treatment*;
  - Etiology: Nervous system pathology, inheritance.

References

1. Xeomin Prescribing Information. Frankfurt, Germany: Merz Pharmaceuticals, LLC; April 2021 Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ccdc3aae-6e2d-4cd0-a51c-8375bfee9458&type=display. Accessed June 2, 2021.
2. Botox Prescribing Information. Madison, NJ: Allergan USA, Inc.; February 2021. Available at: http://www.allergan.com/assets/pdf/botox_pi.pdf. Accessed June 2, 2021.
3. Blitzer A, Friedman A, Michel O, et al. Efficacy and safety of incobotulinumtoxinA for the treatment of sialorrhea in Parkinson's disease (PD) and other neurological conditions: Results of a Phase III, placebo-controlled, randomized, double-blind study. Poster presented at: MDS 2017 (21st International Congress of Parkinson's Disease and Movement Disorders), June 4-8, 2017; Vancouver, BC, Canada. Available at: https://www.mdlinx.com/neurology/conference-abstract.cfm/62345/?conf_id=248681. Accessed June 2, 2021.
4. Seppi K, Chahine L, Chaudhuri R et al. International Parkinson and Movement Disorder Society evidence-based medicine review: Update on treatments for the non-motor symptoms of Parkinson's Disease. 2018. Available at https://www.movementdisorders.org/MDSFiles1/Resources/PDFs/EBM-NMS-Final-Paper-August-2018.pdf. Accessed June 2, 2021.
5. Sridharan K, Sivaramakrishnan G. Pharmacological interventions for treating sialorrhea associated with neurological disorders: A mixed treatment network meta-analysis of randomized controlled trials. Journal of Clinical Neuroscience 51 (2018) 12–17. Available at: https://pubmed.ncbi.nlm.nih.gov/29475576/. Accessed May 24, 2021.
6. Lakraj AA, Moghimi, Jabbari B. Sialorrhea: Anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins 2013, 5, 1010-1031; doi:10.3390/toxins5051010. Available at: https://pubmed.ncbi.nlm.nih.gov/23698357/. Accessed June 2, 2021.
7. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011 October; 26(0 3): S42–S80. Available at: https://pubmed.ncbi.nlm.nih.gov/22021174/. Accessed June 2, 2021.
8. Young CA, Johnson EC, et al. Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. Cochrane Database Syst Rev. 2011 May 11;(5):CD006981. doi: 10.1002/14651858.CD006981.pub2. Accessed June 2, 2021.
9. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update. The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Neurology. 2009; 73:12271233. Available at: https://pubmed.ncbi.nlm.nih.gov/19822873/. Accessed June 2, 2021.
10. Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. May 2008; 70(19): 1707-1714. Available at: https://pubmed.ncbi.nlm.nih.gov/18458231/. Accessed June 2, 2021.

11. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. June 15, 2013; 28(7): 863-873. doi:10.1002/mds.25475. Available at: https://pubmed.ncbi.nlm.nih.gov/23649720/. Accessed June 2, 2021.
12. Simpson DM, Hallett M, Ashman EJ et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016; 86(19): 1818-1826. Available at: https://pubmed.ncbi.nlm.nih.gov/27164716/. Accessed June 2, 2021.
13. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2021. Accessed with subscription at: http://www.clinicalkey.com. Accessed June 04, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Line of Business Policy Applies to was updated from "Commercial, HIM, Medicaid" to "All lines of business". 2. Background was updated to remove "…adult patients with…". 3. Background was updated to include "…in patients 2 years of age and older;" and "Upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy;". 4. Background was updated to include "…in adults" after points "upper limb spasticity", "cervical dystonia", and "blepharospasm". 5. Dosing Information dosing regimen for indication Chronic sialorrhea was updated to remove "The recommended total dose per treatment session is 100 Units". 6. Dosing Information dosing regimen for indication Chronic sialorrhea was updated to include specific adult and pediatric dosing tables. 7. Dosing Information maximum dose for indication Chronic sialorrhea was updated from "One treatment period per weeks 16. / 100 units per treatment session consisting: [Parotid gland(s): 60 units (30 units per side)] ;	06/04/2021	09/14/2021

[Submandibular gland(s): 40 units (20 units per side)]" to "[Adults: Max 100 units per treatment session] ; [Pediatric: 75 units]". 8. Dosing Information dosing regimen for indication Cervical dystonia was updated to include "…Administer no more frequently than every 3 months". 9. Dosing Information dosing regimen for indication Blepharospasm was updated to include "…no more frequently than every 3 months". 10. Dosing Information dosing regimen for indication Upper limb spasticity was updated to include "Adults: the recommended total dose is up to 400 Units, divided among affected muscles / Pediatric Patients, excluding spasticity caused by cerebral palsy: the recommended total dose is 8 Units/kg (maximum 200 Units) per single upper limb or 16 Units/kg (maximum 400 U) in both upper limbs, divided among affected muscles. Administer no more frequently than every 3 months". 11. Dosing Information was updated to include indication "Glabellar Lines" and its subsequent dosing information and maximum dose. 12. Dosage Forms was updated from "Vials: 50 units, 100 units, 200 units" to "Injection: 50 Units, 100 Units, or 200 Units lyophilized powder in a single-dose vial". 13. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 14. Initial Approval Criteria I.A.5 was updated from "Dose does not exceed 100 unites per treatment session" to "Dose does not exceed one of the following (a or b)…". 15. Initial Approval Criteria I.A.5.a-b were updated to include "For Adults: 100 units		

per treatment session" and "For Pediatric: 75 units per treatment session" respectively. 16. Initial Approval Criteria I.D.3 was updated from "Age 18 years of age or older" to "Member meets one of the following (a or b)…" 17. Initial Approval Criteria I.D.3.a-b were updated to include "Age 2 to 17 years of age excluding spasticity caused by cerebral palsy" and "Age ≥ 18 years" respectively. 18. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 19. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to change approval duration units from weeks to days. 20. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 21. Continued Therapy Approval Criteria II.A.5.a was updated from "Chronic sialorrhea: 100 units per treatment session" to "Chronic sialorrhea (i or ii)". 22. Continued Therapy Approval Criteria II.A.5.a.i-ii were updated to include "Adult: 100 units per treatment session" and "Pediatric: 75 units per treatment session" respectively. 23. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 24. Appendix B was updated to include Therapeutic Alternatives table. 25. Appendix B: Therapeutic Alternatives was updated to include alternative drugs Botox® (onabotulinumtoxinA) and Botox cosmetic in addition to their respective dosing regimens and maximum doses.		

26. • Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 27. References were reviewed and updated.		