

Drug formulary listing decision – BOTULINUMTOXIN-A

ONABOTULINUMTOXIN-A, INCOBOTULINUMTOXIN-A, ABOBOTULINUMTOXIN-A

Indication(s)

OnabotulinumtoxinA (Botox®) is indicated for the treatment of blepharospasm/VII nerve disorders, cervical dystonia, focal spasticity (including upper and lower limb spasticity associated with stroke), neurogenic detrusor overactivity, overactive bladder, strabismus, equinus foot deformity, hyperhidrosis of the axilla, and for the prophylaxis of chronic migraines.

IncobotulinumtoxinA (Xeomin®) is indicated for the treatment of blepharospasm and hemifacial spasm, cervical dystonia, and upper limb spasticity associated with stroke.

AbobotulinumtoxinA (Dysport Therapeutic™) is indicated for the treatment of cervical dystonia, focal spasticity affecting the upper and lower limbs, and lower limb spasticity in pediatric patients.

Formulary Status

The Drug Advisory Committee (DAC) recommended that botulinumtoxinA products not be listed for workers with the following conditions: neuropathic pain, low back pain, neck pain, myofascial pain, episodic migraine, or any other headache disorders.

The DAC recommended that botulinumtoxinA products be listed for workers with cervical dystonia, blepharospasm/hemifacial spasm, focal spasticity (including upper & lower limb spasticity), neurogenic detrusor overactivity, and chronic migraine, provided the following criteria are met:

- (a) Product being prescribed has an official indication for use in the above listed condition(s)
- (b) Doses (including initial and maximum recommended doses) for each product should reflect product monograph recommendations
- (c) For neurogenic detrusor overactivity, the following additional criteria must also be met:
 - i. *Patient has a subcervical spinal cord injury; AND*
 - ii. *Patient has not responded to behavioral modifications or anticholinergic medications, and/or is intolerant of anticholinergic medications; AND*

- iii. *Subsequent injections are no less than 36 weeks apart and initial injection must have demonstrated a positive clinical response.*

- (d) For chronic migraine, the following additional criteria must also be met:

- i. *Patient is experiencing chronic migraine (≥15 days/month, with continuous headache lasting ≥4 hours and ≥4 distinct headache episodes each lasting ≥4 hours); AND*
- ii. *Patient has failed* 3+ oral prophylactic medications†; AND*
- iii. *Botox® is being requested by a physician with training in management of headache, and will be administered by a physician with appropriate qualifications & experience.*

**failure being defined as <30% reduction in frequency of headache days to an adequate dose and duration of 3 prophylactic therapies (2 treatments must be of different classes, and contraindications or intolerable adverse effects will only be considered for 1 of 3 medications)*

†Beta-blockers, TCAs, verapamil/flunarizine, sodium valproate/divalproex sodium, topiramate, gabapentin

Notes regarding continued therapy with Botox® for chronic migraine prophylaxis:

- *Patients with an inadequate response (<50% reduction in headache days per month) after two treatment cycles should be discontinued from further Botox® therapy.*
- *Patients with an adequate response who transition from chronic to episodic migraine should also be discontinued off Botox® within 3 months of that transition.*

Criteria for resumption of Botox® for chronic migraine prophylaxis (Renewal Criteria):

- i. *Objective evidence (i.e. headache diary) that the patient has obtained an adequate treatment response; AND*
- ii. *Confirmation that the patient has reverted back to chronic migraine upon trial discontinuation.*

WSIB accepts the DAC recommendations. Botox®, Xeomin®, and Dysport Therapeutic™ will be listed on the CNS/PNS (03WS), Facial/EENT injury (04WS), Cardiovascular (14WS), and Serious Injury (27WS) formularies.

Recommendation highlights

- BotulinumtoxinA is a neurotoxin derived from *Clostridium botulinum*, which causes temporary paralysis when injected into a muscle.
- An external, independent review of botulinumtoxinA in 2019 assessed data regarding the efficacy and safety of botulinumtoxinA for the following conditions: cervical dystonia; spasticity disorders (blepharospasm, hemifacial spasm, other spastic disorders); pain syndromes (neuropathic pain, neck pain, back pain, and myofascial pain); headache (both migraine and non-migraine); stroke; and neurogenic detrusor overactivity.
- The review concluded that there were no high quality studies available demonstrating that botulinumtoxinA is effective in reducing neck pain, back pain, myofascial pain or neuropathic pain. The Canadian Pain Society 2014 Consensus Statement on Chronic Neuropathic Pain classifies botulinumtoxin as a fourth-line agent for the management of neuropathic pain based on evidence from two small studies which were acknowledged to be likely underpowered.
- There was insufficient evidence to recommend botulinumtoxinA for headache disorders, including chronic tension-type headaches, cluster headaches, chronic daily headaches, or episodic migraine.
- Numerous guidelines consider botulinumtoxinA a first-line agent for cervical dystonia, blepharospasm and hemifacial spasm due to established efficacy in clinical trials and the absence of comparable therapeutic alternatives for these conditions.
- The available evidence suggests that botulinumtoxinA products are effective for treating spasticity disorders caused by stroke or other brain trauma. However, there is a lack of comparative head-to-head trials comparing botulinumtoxinA products to each other or to other active comparators for these conditions.
- Botox® is the only botulinumtoxinA product indicated for neurogenic detrusor overactivity. Randomized, controlled trials have demonstrated that Botox® may be effective for reducing symptoms of neurogenic detrusor overactivity, and clinical guidelines suggest that it may be considered in patients who have failed an adequate trial of anticholinergic medication and behavioral modifications.
- Botox® is the only botulinumtoxinA product indicated for prophylaxis of chronic migraines. A Cochrane Review from 2018 established that there is moderate-quality evidence Botox® may reduce the number of migraine days per month by 2 days compared to placebo. However, there is a lack of consensus from clinical guidelines on the place in therapy of Botox® for chronic migraine prophylaxis.
- BotulinumtoxinA is generally considered safe when properly dosed and administered. Most of the side effects are self-limiting and transient. However, there have been rare cases of distant spread of toxin to other parts of the body, which may cause serious side effects such as breathing difficulties.
- There was limited pharmacoeconomic study data relevant to the WSIB worker population that compared botulinumtoxinA products to conventional therapies. In conditions for which alternatives to botulinumtoxinA products exist, all botulinumtoxinA products are significantly more expensive than these alternatives.
- The Ontario Drug Benefit Program funds indicated botulinumtoxinA products under Limited Use criteria for cervical dystonia, blepharospasm/hemifacial spasm, focal spasticity (including upper and lower limb spasticity), and neurogenic detrusor overactivity, and under Exceptional Access Program for the prophylaxis of chronic migraines.
- Based on published evidence and guideline recommendations, the DAC recommended that botulinumtoxinA products be listed only for cervical dystonia, blepharospasm, hemifacial spasm, focal spasticity (including upper and lower limb spasticity), neurogenic detrusor overactivity, and for the prophylaxis of chronic migraines. The DAC further recommended that the products be listed based on their approved indications, and that doses be limited to those recommended in each products' respective monographs. For neurogenic detrusor overactivity and chronic migraine, the DAC recommended that WSIB follow current Ontario Drug Benefit criteria (listed in the 'Formulary Status' section above).

Products available in Canada:

OnabotulinumtoxinA - Botox®
IncobotulinumtoxinA – Xeomin®
AbobotulinumtoxinA - Dysport Therapeutic™