BOTOX®
onabotulinumtoxinA

CONSIDER THE EXPERIENCE OF BOTOX®

Available in Canada for

21+ years (upper limb spasticity)

3+ years (lower limb spasticity)

[Pr]BOTOX® (onabotulinumtoxinA for injection) is indicated:

- In the management of focal spasticity, including the treatment of upper limb spasticity associated with stroke in adults
- For the symptomatic treatment of lower limb spasticity associated with stroke in adults

REFERENCE: BOTOX Product Monograph, Allergan Inc. March 11, 2021.

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DO YOU SEE PATIENTS LIKE PETER?

This is Peter, 63, who experienced multiple hemorrhagic strokes last year*.

He started noticing spasticity develop on the right side of his body just 3 months after his stroke.

How can we help Peter?

*"Peter" is for illustrative purposes only. Might not be representative of all patients.

IN A THREE-MONTH, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, INCLUDING 126 PATIENTS WITH UPPER LIMB POST-STROKE SPASTICITY,

BOTOX REDUCED MUSCLE TONE IN SPASTIC UPPER LIMBS VS PLACEBO AS MEASURED ON THE ASHWORTH SCALE 12 WEEKS POST-TREATMENT[1,2]*

Muscle tone: Changes in mean scores on the Ashworth Scale observed at Week 12 for the following therapeutic targets†‡:

WRIST FLEXOR	**-1.07** (95% CI: -1.30, -0.84) with BOTOX	**VS**	**-0.31** (95% CI: -0.48, -0.14) with placebo (p<0.001)
FINGER FLEXOR	**-0.78** (95% CI: -1.05, -0.51) with BOTOX	**VS**	**-0.12** (95% CI: -0.32, -0.08) with placebo (p<0.001)
THUMB FLEXOR	**-0.92** (95% CI: -1.27, -0.56) with BOTOX	**VS**	**-0.31** (95% CI: -0.62, 0.01) with placebo (p=0.02)

Adapted from Brashear, *et al.*

CI: Confidence interval.
FS: Focal spasticity.
*Results from a 3-month, double-blind, placebo-controlled study in which patients with upper limb spasticity post-stroke (n=126) were treated with 200 U to 240 U of BOTOX into the wrist, finger and thumb flexor muscles.
†For the principal therapeutic target and the muscle tone score, the data shown are changes from the baseline scores.
‡Muscle tone was measured using the Ashworth scale. A score of 0 denotes no increase in muscle tone, 1 a slight increase, 2 a more marked increase, 3 a considerable increase and 4 rigid flexion.

ADULT FS: UPPER LIMB
ADULT FS: LOWER LIMB

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IN A THREE-MONTH, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, INCLUDING 126 PATIENTS WITH UPPER LIMB POST-STROKE SPASTICITY,

BOTOX DEMONSTRATED SIGNIFICANTLY GREATER IMPROVEMENTS IN MEAN DAS SCORES VS PLACEBO[1,2]*

Changes in mean DAS scores on principal therapeutic target observed at Week 12:

-0.88
(95% CI: -1.12, -0.63)
with BOTOX

VS

-0.46
(95% CI: -0.67, -0.24)
with placebo (p=0.02)†‡

At 6 weeks:

62%
(n=40) of BOTOX-treated patients showed improvement in the principal treatment target

VS

27%
(n=17) of placebo-treated patients (p<0.001)

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‡The principal therapeutic target was chosen by each patient and a study investigator, and the effect of treatment on this target was measured with the use of the Disability Assessment Scale. A score of 0 indicates no disability, 1 mild disability, 2 moderate disability and 3 severe disability. Thirty-two percent of the patients chose dressing, 30% chose limb position, 26% chose hygiene and 12% chose pain as the principal therapeutic target.

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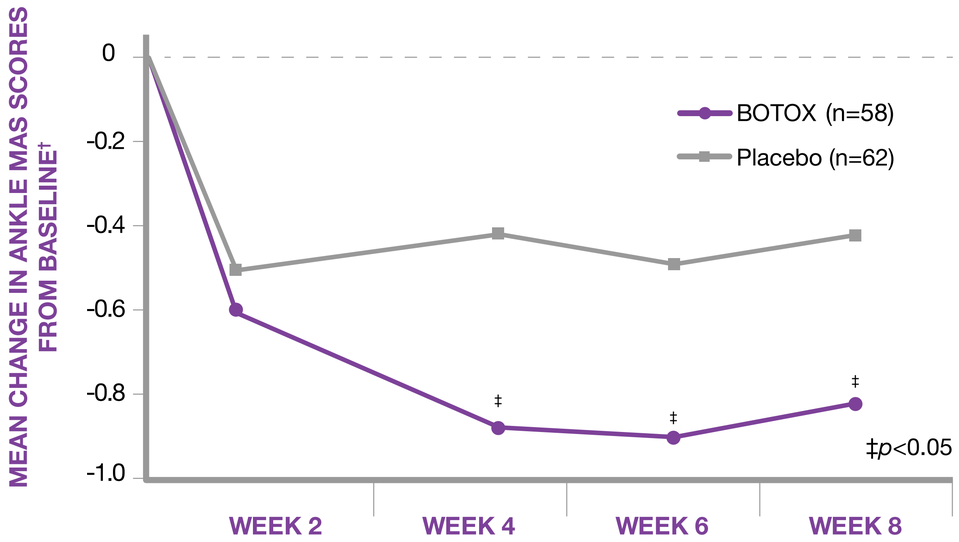
IN A MULTICENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, INCLUDING 120 PATIENTS WITH POST-STROKE LOWER LIMB SPASTICITY,

BOTOX SIGNIFICANTLY REDUCED THE MEAN CHANGE FROM BASELINE IN MAS ANKLE SCORES COMPARED TO PLACEBO AT WEEKS 4, 6 AND 8*

Secondary endpoint: Mean change in ankle MAS scores



Adapted from Kaji, *et al*.

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ADULT FS: LOWER LIMB

FS: Focal spasticity.
MAS: Modified Ashworth Scale.
*Results from a multicentre, randomized, parallel-group, double-blind, phase 3 placebo-controlled trial in which patients with post-stroke lower limb spasticity (N=120) were randomized 1:1 to receive a single injection of BOTOX (300 U) or placebo.
†Efficacy was measured using the MAS – a 6-point nominal scale using subjective clinical assessments of tone ranging from 0 (no increases in tone) to 4 (limb rigid in flexion or extension [abduction/adduction]). Patients were followed for 12 weeks.

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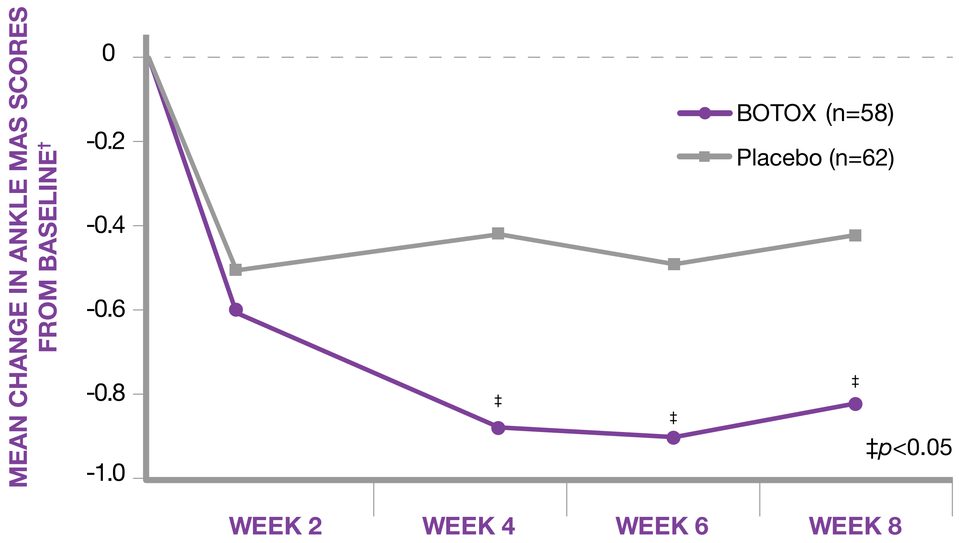

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IN A THREE-MONTH, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, INCLUDING 468 PATIENTS WITH LOWER LIMB POST-STROKE SPASTICITY,

BOTOX REDUCED MUSCLE TONE VS PLACEBO[1,2]*

LS mean changes from baseline in ankle plantar flexors in MAS score (average score observed at Weeks 4 and 6):

-0.81
with BOTOX ITT
(n=233)

VS

-0.61
with placebo
(n=235)

(Difference: -0.2; 95% CI: -0.356, -0.050; *p*=0.010)†‡§

CGI: Clinical Global Impression.
CI: Confidence interval.
FS: Focal spasticity.
ITT: Intent-to-treat.
LS: Least squares.
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†Muscle tone was measured using the MAS. The MAS uses a similar scoring system as the Ashworth scale. A score of 0 denotes no increase in muscle tone, 1 an increase in muscle tone manifested by a catch and release or by minimal resistance at the end of the range of motion, 1+ slight increase in muscle tone manifested by a catch followed by minimal resistance throughout the remainder of the range of movement, 2 a more marked increase, 3 a considerable increase and 4 rigid flexion.
‡*P*-values and 95% CIs for between-group comparisons were obtained from an ANCOVA model including treatment and centre as factors, with baseline ankle MAS-B and muscle groups injected as covariates. Estimated differences were based on the LS means.
§To control the type 1 error rate for multiple secondary endpoints, a gatekeeping approach was used. The first secondary endpoint (CGI) could only indicate significance if the primary endpoint (MAS-B) was significant. CGI employs a 9-point scale from -4 (very marked worsening) to +4 (very marked improvement).

ADULT FS: UPPER LIMB
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IN A THREE-MONTH, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, INCLUDING 468 PATIENTS WITH LOWER LIMB POST-STROKE SPASTICITY,

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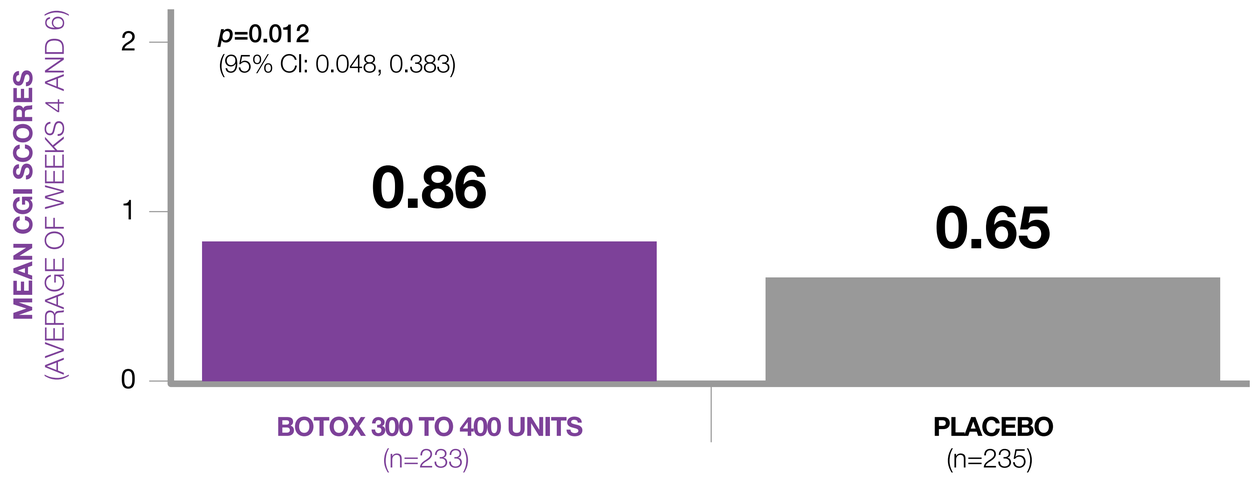
IN A THREE-MONTH, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, INCLUDING 468 PATIENTS WITH LOWER LIMB POST-STROKE SPASTICITY,

BOTOX DEMONSTRATED SIGNIFICANTLY GREATER IMPROVEMENTS IN AVERAGE LS MEAN CGI SCORES VS PLACEBO[1,2]*

Secondary endpoint: Mean CGI scores with BOTOX vs placebo at weeks 4 and 6†‡



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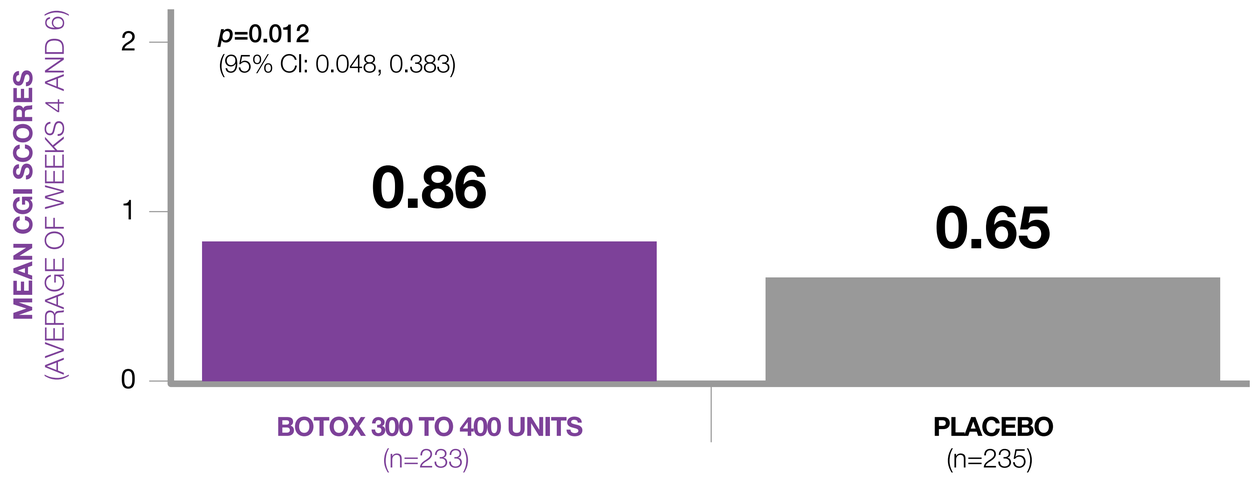

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BOTOX: DEMONSTRATED SAFETY PROFILE

ADULT UPPER LIMB SPASTICITY

The following adverse events (AEs) were commonly reported in double-blind and open-label studies involving 399 patients treated with BOTOX:

- Hypertonia
- Ecchymosis
- Muscular weakness
- Pain in extremity
- Injection pain
- Pyrexia
- Influenza-like illness

ADULT LOWER LIMB SPASTICITY

A total of 538 patients have been treated with BOTOX for lower limb spasticity in 7 double-blind, placebo-controlled studies.

The most frequently reported adverse events in patients treated in the All BOTOX group were:

- Fall (4.5% in both BOTOX groups and placebo)
- Pain in extremity (5.0% in BOTOX groups vs 4.7% in placebo)

Adverse events reported in ≥2% of BOTOX-treated patients and more frequently than in placebo-treated patients – a single-dose placebo-controlled study (first 12 weeks of double-blind phase)

ADVERSE REACTION	BOTOX (300–400 units) (n=231)	PLACEBO (n=233)
Arthralgia	4%	1%
Back pain	3%	2%
Myalgia	2%	1%
Upper respiratory tract infection	2%	1%
Injection site pain	2%	1%

Adapted from the BOTOX Product Monograph, 2021.

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THE FORMATION OF NEUTRALIZING ANTIBODIES TO BOTOX MAY REDUCE THE EFFECTIVENESS OF TREATMENT BY INACTIVATING THE BIOLOGICAL ACTIVITY OF THE TOXIN

- The proportion of patients who lose their response to botulinum toxin therapy and have demonstrable levels of neutralizing antibodies is small
- There have been patients, in whom neutralizing antibodies had been detected, who continued to respond to therapy

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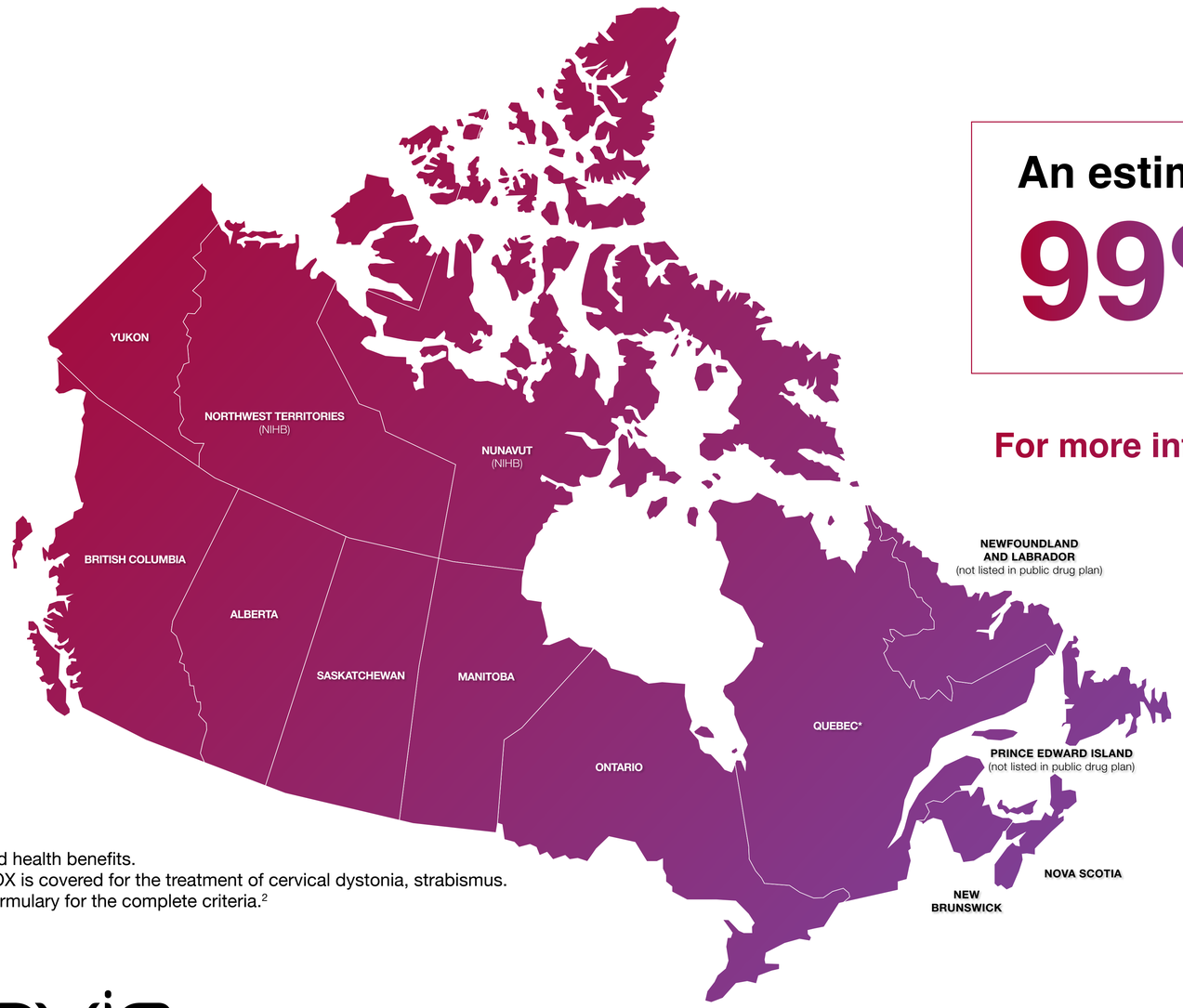
BOTOX COVERAGE INFORMATION

BOTOX IS AVAILABLE ON MOST PUBLIC AND PRIVATE INSURANCE PLANS (CRITERIA MAY APPLY)



An estimated

99% of Canadians with private insurance have access to coverage (restricted and unrestricted) for BOTOX in the treatment of focal spasticity.[1]

For more information, refer to the coverage listings available for each province.

NIHB: Non-insured health benefits.
*In Quebec, BOTOX is covered for the treatment of cervical dystonia, strabismus. Please see the formulary for the complete criteria.[2]

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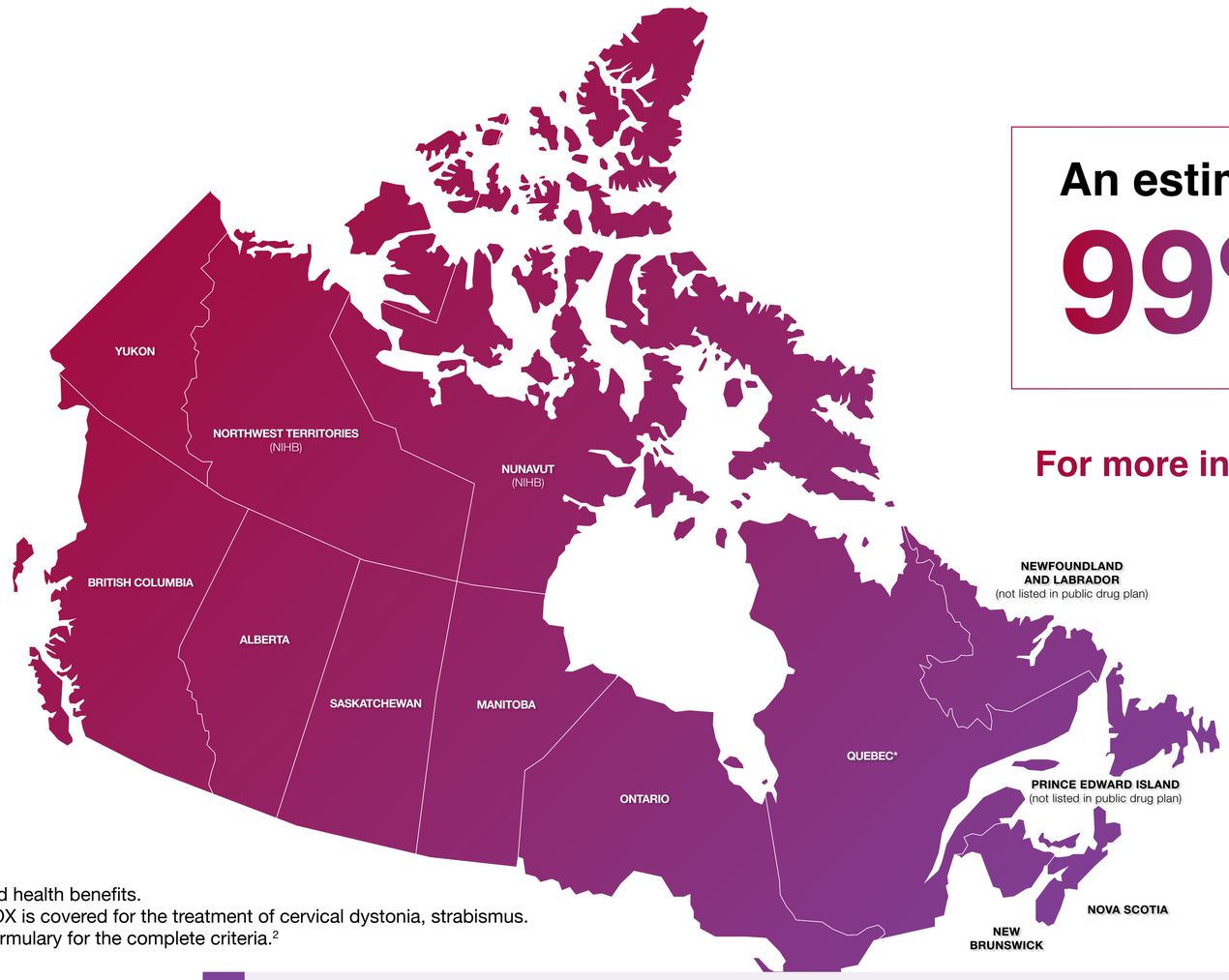

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CONSIDER THE EXPERIENCE OF BOTOX

BOTOX DEMONSTRATED EFFICACY IN POST-STROKE SPASTICITY IN BOTH THE UPPER AND LOWER LIMB[1-3]

BOTOX reduced muscle tone vs placebo

- Upper limb: Mean changes on the Ashworth scale for wrist flexor (-1.07 vs -0.31, respectively, $p<0.001$); finger flexor (-0.78 vs -0.12, respectively, $p<0.001$); thumb flexor (-0.92 vs -0.31, respectively, $p=0.02$) at Week 12[1*]
- Lower limb: LS mean changes from baseline in ankle plantar flexors in MAS score (-0.81 vs -0.61 respectively, $p=0.010$) at Weeks 4 and 6[1†]

BOTOX helped significantly more patients achieve improvements in their selected treatment targets

- 62% of wrist, finger and thumb spasticity patients reported improvements in mean DAS score on the principal treatment target at Week 6 (n=40, $p<0.001$ vs placebo)[2*]
- Patients with lower limb spasticity reported improvements in average LS mean CGI scores with BOTOX vs placebo at Weeks 4 and 6 (0.86 vs 0.65, $p=0.012$)[1,3†]

BOTOX IS AVAILABLE ON MOST PUBLIC AND PRIVATE INSURANCE PLANS (CRITERIA MAY APPLY).‡

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‡Newfoundland and Prince Edward Island excluded from public listing.

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BOTOX DEMONSTRATED EFFICACY IN POST-STROKE SPASTICITY IN BOTH THE UPPER AND LOWER LIMB[1-3]

BOTOX reduced muscle tone vs placebo

- Upper limb: Mean changes on the Ashworth scale for wrist flexor (-1.07 vs -0.31, respectively, $p<0.001$); finger flexor (-0.78 vs -0.12, respectively, $p<0.001$); thumb flexor (-0.92 vs -0.31, respectively, $p=0.02$) at Week 12[1]*
- Lower limb: LS mean changes from baseline in ankle plantar flexors in MAS score (-0.81 vs -0.61, respectively, $p=0.010$) at Weeks 4 and 6[1†]

BOTOX helped significantly more patients achieve improvements in their selected treatment targets

- 62% of wrist, finger and thumb spasticity patients reported improvements in mean DAS score on the principal treatment target at Week 6 (n=40, $p<0.001$ vs placebo)[2]*
- Patients with lower limb spasticity reported improvements in average LS mean CGI scores with BOTOX vs placebo at Weeks 4 and 6 (0.86 vs 0.65, $p=0.012$)[1,3†]

BOTOX IS AVAILABLE ON MOST PUBLIC AND PRIVATE INSURANCE PLANS (CRITERIA MAY APPLY).‡

CGI: Clinical Global Impression.
DAS: Disability Assessment Scale.
LS: Least squares.
MAS: Modified Ashworth Scale.

*Results from a 3-month, double-blind, placebo-controlled study in which patients with upper limb spasticity post-stroke (N=126) were treated with 200 U to 240 U of BOTOX into the wrist, finger and thumb flexor muscles.
†Results from a randomized, multicentre, double-blind, placebo-controlled study including 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (MAS score of at least 3) and who were at least 3 months post-stroke. Patients received 300 to 400 units of BOTOX or placebo and were injected intramuscularly into the study mandatory muscles: gastrocnemius, soleus and tibialis posterior and optional muscles including flexor halluces longus, flexor digitorum longus, flexor digitorum brevis, extensor halluces and rectus femoris. Patients were followed for 12 weeks.
‡Newfoundland and Prince Edward Island excluded from public listing.

REFERENCES:
1. BOTOX Product Monograph, Allergan Inc. March 11, 2021. **2.** Brashear A, Gordon MF, Elovic E, *et al.* Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002;347:395–400. **3.** Wein T, Esquenazi A, Jost WH, *et al.* OnabotulinumtoxinA for the treatment of poststroke distal lower limb spasticity: A randomized trial. *PM&R* 2018;10:693–703.

Clinical use:

BOTOX is not intended as a replacement for usual standard of care regimens and is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

Studies specifically designed to determine the dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. Initial dosing should begin at the lowest recommended dose for the specific indication.

Contraindications:

- Patients who are hypersensitive to any botulinum toxin type A or to any ingredient in the formulation or component of the container
- The presence of infection at the proposed injection site(s)

Most serious warnings and precautions:

Not interchangeable: The term "Allergan unit" upon which dosing is based is a specific measurement of toxin activity that is unique to Allergan's formulation of botulinum toxin A. Therefore, the "Allergan units" used to describe BOTOX activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX activity are not interchangeable with other products.

Appropriate qualification and experience: BOTOX should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.

Follow the recommended dosage and frequency of administration for BOTOX.

Distant spread of toxin effect: The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

Other warnings and precautions:

- Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach; some patients had pre-existing dysphagia or significant debility
- Pneumothorax associated with injection procedure has been reported following administration near the thorax; caution is warranted when injecting in proximity to the lung, particularly the apices
- Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle
- Muscle weakness remote to the site of injection and other serious adverse effects (e.g., dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, in some cases associated with a fatal outcome
- Patients with a history of underlying neurological disorders, dysphagia and/or aspiration should be treated with extreme caution. The botulinum toxin product should be used under specialist supervision in these patients and only if the benefit is considered to outweigh the risk
- Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise
- Cardiovascular events: There have been reports following administration of botulinum toxin of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The exact relationship with BOTOX is unknown
- Immune: Formation of neutralizing antibodies to botulinum toxin A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin
- Anaphylactic reactions: As with all biologic products, an anaphylactic reaction may occur, necessary precautions should be taken and epinephrine should be available
- Neurologic: Extreme caution should be exercised with administering BOTOX to individuals with peripheral motor neuropathic disorders or neuromuscular junction disorders. These patients may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX, in some cases requiring placement of a gastric feeding tube. When exposed to very high doses, patients with neurologic disorders (e.g., pediatric cerebral palsy or adult spasticity) may also be at increased risk of clinically significant systemic effects
- New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events
- Skin: As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with the injection
- Special populations: BOTOX should not be used during pregnancy unless clearly necessary. Caution should be exercised when BOTOX is administered to a nursing woman

For more information:

Please consult the Product Monograph at: https://pdf.hres.ca/dpd_pm/00060199.PDF for important information relating to adverse reactions, interactions and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling: 1-800-668-6424.

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