

CEDAC FINAL RECOMMENDATION

CLOSTRIDIUM BOTULINUM NEUROTOXIN TYPE A, FREE FROM COMPLEXING PROTEINS (Xeomin – Merz Pharma Canada Ltd.) Indication: Post-stroke Spasticity

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Xeomin not be listed for post-stroke spasticity of the upper limb.

Reasons for the Recommendation:

1. There are no head to head trials comparing Xeomin and Botox in the treatment of post-stroke spasticity of the upper limb; therefore, the comparative efficacy of Xeomin with Botox is uncertain for this condition.
2. The one randomized placebo controlled trial (N = 148) included in the systematic review of Xeomin for post-stroke spasticity, reported that Xeomin was statistically significantly better than placebo in the proportion of patients improving one point on the Ashworth scale, which measures spasticity. However, the Ashworth scale correlates poorly with functional outcomes. The impact of Xeomin on functional outcomes was not clear in patients with post-stroke spasticity of the upper limb and quality of life was not measured.

Of Note:

In light of the Committee's reasons for the recommendation, drug plans may wish to review evidence for the impact of all botulinum toxin A therapies on functional outcomes and quality of life in patients with post-stroke spasticity of the upper limb.

Background:

Xeomin is a botulinum toxin A formulation that has Health Canada indications for the treatment of blepharospasm, cervical dystonia of a predominantly rotational form (i.e., spasmodic torticollis), and post-stroke spasticity of the upper limb. The focus of this recommendation is post-stroke spasticity of the upper limb.

Botulinum toxin A is a neurotoxin that inhibits acetylcholine release at the neuromuscular junction, temporarily preventing muscle contractions. Xeomin differs from Botox, the only other botulinum toxin A product available in Canada, in that it is free from complexing proteins.

Common Drug Review

Xeomin is given as an intramuscular injection and is available as a powder for reconstitution (100 U per vial). The Health Canada product monograph recommends that dosing in post-stroke spasticity of the upper limb be individualized based on the muscle to be injected (10 to 80 U per muscle). A total dose should not exceed 400 U. The recommended interval between each treatment session is at least 12 weeks.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review: a systematic review of randomized controlled trials (RCTs) of Xeomin and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials

The CDR systematic review included one RCT in patients with post-stroke spasticity of the upper limb, the Kanovsky study. No active comparator trials were identified. The one manufacturer-sponsored, double-blind, randomized, placebo-controlled superiority trial evaluated the efficacy of Xeomin in 148 patients with post-stroke (\geq six months) spasticity of the upper limb. Approximately 25% of patients had been previously treated with botulinum toxin A, and about 75% were treatment naïve. Doses per patient ranged from 170 U to 400 U (mean dose 306 U). Doses per patient could not exceed 400 U, which resulted in one-third of the patients receiving only partial therapy, as not all affected muscles could be injected. The trial evaluated the effect of one treatment at four weeks and patients were followed for up to 20 weeks. After 12 weeks, patients had the option to request another treatment. Patients could continue in an open-label extension phase where they received up to five Xeomin treatments over 48 to 69 weeks. Although permitted, the use of concomitant non-pharmacologic treatment options was less than 40% in the trial. Across treatment groups, 16% to 23% of patients received physiotherapy, 4% to 5% received occupational therapy and 8% to 12% received rehabilitation therapy. Withdrawals were low ($<$ 3%) and similar between treatment groups.

Outcomes

The primary outcome of the trial was the proportion of patients experiencing a one point improvement from baseline in the Ashworth scale for wrist flexors at four weeks.

- The Ashworth scale is an ordinal four point scale used to measure the degree of spasticity with a score ranging from zero (no increase in tone) to four (limb rigid in flexion or extension). The validity of the scale has been criticized because it measures resistance to passive movement, which may be attributed to factors other than spasticity and because it does not provide information on functional abilities. The minimal clinically important difference for this scale is unknown but a one point change has been reported as clinically relevant.

In addition, the Committee discussed the following outcomes included in the CDR systematic review: the Disability Assessment Scale, the Carer Burden Scale, global assessments of efficacy by patient, investigator and caregiver, and duration of treatment effect. Quality of life was not measured.

- The Disability Assessment Scale assesses impairment in the following four domains: hygiene, dressing, limb position and pain. One of the domains may be

selected as the principal therapeutic target for treatment. Good intra- and inter-rater reliability have been demonstrated with both the Disability Assessment Scale and Ashworth scale.

- The Carer Burden Scale measures the physical burden of caring for someone with upper limb spasticity. The carer rates the degree of difficulty associated with four items related to the affected limb (e.g., cleaning the palm of the hand, cutting fingernails, cleaning the armpit, putting the arm through a sleeve). In the Kanovsky study, a fifth domain was also measured, applying a splint. Item scores are summed and averaged with total scores ranging from zero to four with higher scores indicating a greater burden. No information on validity or reliability was identified.

Results

Efficacy or Effectiveness

- A statistically significantly greater proportion of patients had a one point improvement in the Ashworth scale for wrist flexors in the Xeomin group compared with placebo at week four (68.5% versus 37.3%, odds ratio 3.97, 95% CI: 1.90 to 8.30).
- There was a statistically significant improvement with Xeomin compared with placebo on the Disability Assessment Scale for the domains of hygiene, limb position and pain, but not for dressing. The majority of patients, 40.5%, chose dressing as the target domain they would like to improve. There was a statistically significant improvement with Xeomin compared with placebo for the target domain (45.2% versus 21.3%, $P = 0.002$) but it was not reported as to how many of those achieving their target domain were among the 40.5% of patients who wanted to improve dressing.
- At week four, only two out of five items from the Carer Burden Scale were statistically improved with Xeomin compared with placebo: cleaning the palm of the hand and putting the arm in a sleeve. The reliability and validity of this scale has not been studied and the subjective nature of this outcome reduces confidence in these results.
- The duration of treatment effect was statistically significantly greater with Xeomin compared with placebo by three days (87 days versus 84 days, $P = 0.004$), however the clinical relevance of this analysis is uncertain and the interpretation is limited given that based on the study protocol another treatment could not be requested any earlier than 84 days (i.e., 12 weeks).
- Errors in blood sampling compromised the quality of antibody data, therefore, it is not clear if the finding that no patients had neutralizing antibodies is valid.

Harms (Safety and Tolerability)

- Serious adverse events, adverse events, withdrawals due to adverse events and adverse events possibly related to the diffusion of toxin were similar between the Xeomin and placebo groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of Xeomin and Botox for the treatment of post-stroke spasticity of the upper limb. In the absence of head to head randomized controlled trials of Xeomin and Botox for post-stroke spasticity of the upper limb, the manufacturer based their claims of similar clinical efficacy, safety and dosing on an indirect comparison, which included

one randomized placebo controlled trial for Xeomin and only one of many published trials available for Botox, the Brashear study.

The studies selected by the manufacturer for the indirect comparison were not sufficiently similar to establish one-to-one dosing. There were differences in the two trial protocols with respect to maximum botulinum toxin A doses permitted for Xeomin and Botox (400 U versus 240 U, respectively) and in which muscles it could be injected. Xeomin is priced lower (\$330) than Botox (\$357) per 100 U vial, however, it is uncertain whether the lower price of Xeomin will necessarily lead to cost savings if dose equivalence is uncertain for this indication.

Other Discussion Points:

- The Committee discussed that therapeutic options for post stroke spasticity of the upper limb include occupational and physiotherapy, surgical interventions and oral medications but that a large proportion of patients in the trials did not appear to be using non-pharmacologic treatment options.
- Post-stroke spasticity of the upper limb is a result of upper motor neuron injury. Because there are many components of motor neuron damage, treatment of only post-stroke spasticity of the upper limb will not result in regaining full functionality. In addition, spasticity due to fixed contractures will not be affected by treatment with Xeomin, similar to Botox.
- Published systematic reviews of placebo-controlled trials of botulinum toxins have not clearly and consistently demonstrated an impact on functional outcomes and quality of life in patients with post-stroke spasticity of the upper limb.
- The product monograph for Xeomin notes that unit doses recommended for Xeomin are not interchangeable with those for other preparations of botulinum toxin, including Botox. Similar statements are made in the product monographs of other botulinum toxin A formulations.
- Errors in blood sampling that compromised the quality of antibody data in the randomized phase of the Kanovsky study were resolved during the open-label extension phase and no antibodies were detected at any point. The Committee discussed that comparative antibody data with Botox was not provided, therefore, there is still insufficient evidence to conclude that because Xeomin has less complexing proteins, it is less immunogenic than Botox.
- Uncertainty around comparative dosing of Xeomin and Botox in the placebo-controlled trial of Xeomin and the one placebo-controlled trial of Botox that the manufacturer considered in the indirect comparison was discussed. In both studies, dosing was protocol-driven and different maximum doses were permitted (400 U versus 240 U, respectively).

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

None.

Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

Common Drug Review

About this Document:

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CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

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