



CEDAC FINAL RECOMMENDATION

CLOSTRIDIUM BOTULINUM NEUROTOXIN TYPE A, FREE FROM COMPLEXING PROTEINS (Xeomin – Merz Pharma Canada Ltd.) Indication: Cervical Dystonia (Spasmodic Torticollis)

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Xeomin be listed similar to the way drug plans currently list Botox for cervical dystonia of the predominantly rotational form (i.e., spasmodic torticollis).

Reasons for the Recommendation:

1. The Committee considered that in the treatment of cervical dystonia, efficacy of Xeomin was similar to Botox. This was based on the results of a randomized controlled trial demonstrating that Xeomin was non-inferior to Botox with respect to the change from baseline in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity score, a measure of cervical dystonia symptoms. Harms, including adverse events potentially related to toxin diffusion, also appeared similar between Xeomin and Botox.
2. Xeomin (\$330 per 100 unit vial) is less expensive than Botox (\$357 per 100 unit vial).

Of Note:

There is no evidence that sequential use of Xeomin would be effective in individuals where Botox has not provided the desired therapeutic effect as patients included in the Xeomin trials for cervical dystonia were either naïve to botulinum toxin or had a stable therapeutic response to botulinum toxin.

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 (spasmodic torticollis) and post-stroke spasticity of the upper limb. The focus of this recommendation is the cervical dystonia indication.

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.

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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 cervical dystonia be individualized based on the muscle to be injected, up to a maximum of 50 U per injection site. A total dose does not usually exceed 200 U, but up to 300 U may be used. The recommended interval between each treatment is at least three months.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): 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 three RCTs of patients with cervical dystonia: one placebo-controlled trial and two trials comparing Xeomin with Botox. All trials were manufacturer-sponsored and all included only patients with cervical dystonia of the predominantly rotational form.

- The Benecke study (N = 466) was a double blind randomized controlled non-inferiority trial comparing Xeomin with Botox in patients who were successfully pretreated with botulinum toxin and had a stable therapeutic response. The effects of one treatment were evaluated at four weeks and patients were followed to a maximum of 16 weeks.
- Study 408 (N = 233) is an unpublished double-blind randomized placebo-controlled trial that evaluated the superiority of fixed doses of Xeomin (120 U and 240 U, total dose) compared with placebo. The effects of one treatment were evaluated at four and eight weeks and patients were followed to a maximum of 20 weeks. Approximately 40% of patients were treatment-naïve and the remainder were pretreated with botulinum toxin.
- Study 9801 (N = 53) is an unpublished, open-label, dose-ranging trial that evaluated Xeomin injected into two muscles in fixed doses. This study was of two weeks duration with an uncontrolled follow-up to 120 days. The primary outcome was the change from baseline in compounded muscle action potential during maximum activation in the sternocleidomastoid muscle at week two. The relevance of this study is limited by its design and small sample size therefore it was not emphasized during the Committee's deliberations.

In the Benecke study and Study 408, patients were allowed to continue on stable doses of any drug to treat focal dystonias. Withdrawals were low across all three studies. The trials were too short to appropriately assess the development of neutralizing antibodies, long-term harms or duration of therapy.

Outcomes

The primary outcome of the Benecke trial was the change from baseline in TWSTRS severity subscore at week four. The primary outcome of Study 408, the placebo-controlled trial, was the change from baseline in the total TWSTRS score at week four.

- The total TWSTRS score quantifies the disease burden associated with cervical dystonia and ranges from zero to 85 with higher scores indicating a greater disease burden. It is composed of three subscales: severity (scores from zero to 35), disability (scores from zero to 30) and pain (scores from zero to 20).

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The scale has been validated in patients treated with Botox but there is no information on what is a minimal clinically important difference for either the total score or any of the subscores.

In addition, the Committee discussed the following outcomes included in the CDR systematic review: global assessment of efficacy, presence of neutralizing antibodies, dysphagia and duration of treatment effect. Quality of life and functional outcomes were not measured in any of the trials.

Results

Efficacy or Effectiveness

- In the Benecke study, Xeomin was non-inferior to Botox based on the primary outcome, change in mean TWSTRS severity subscale at week four ($\Delta = -0.33$, 95% CI: -1.0 to 0.38). There were no statistically significant differences between Xeomin and Botox in the mean TWSTRS pain subscale or global efficacy assessments, although it was noted that pain scores at baseline were very low and effects would be difficult to detect. The total TWSTRS scale and TWSTRS disability subscales were not reported.
- Study 408, demonstrated that Xeomin was better than placebo. There was a statistically significant improvement in change in mean total TWSTRS scores at week four (primary outcome) for both Xeomin 240 U ($\Delta = -9.0$, 95% CI: -12.0 to -5.9) and Xeomin 120 U ($\Delta = -7.5$, 95% CI: -10.4 to -4.6) when compared with placebo. Xeomin was also statistically significantly better than placebo for all TWSTRS subscale scores.
 - A manufacturer pre-specified subgroup analysis of pre-treated and treatment naïve patients based on mean Total TWSTRS scores found that the treatment effect for pre-treated patients appeared higher at the 240 U dose compared with the 120U dose, but formal statistical tests for interaction were not conducted.

Harms (Safety and Tolerability)

- Serious adverse events (ranging from 0% to 8.3%) and withdrawals due to adverse events were low and similar across treatment groups and studies.
- Adverse events were not statistically significantly different between Xeomin and Botox in the Benecke study (28% versus 24%, respectively) or between Xeomin 240 U and Xeomin 120 U compared with placebo in Study 408 (56% and 56% versus 42%, respectively). Among treatment naïve patients in Study 408, more patients experienced adverse events in the high dose Xeomin group than the low dose Xeomin group or placebo (71%, 58% and 53%, respectively).
- In the Benecke study, adverse events indicating possible toxin diffusion, including dysphagia, were higher, but not statistically significantly different in the Xeomin group compared with Botox (13.0% versus 9.1%, respectively). Dysphagia appeared to be dose related in Study 408 (up to 18.5%), but all events were considered mild.
- The proportion of patients developing neutralizing antibodies was low in the Benecke study and in Study 408. In the Benecke study, there were six patients who were newly positive for neutralising antibodies at the final visit, two Xeomin patients and four Botox patients. Not all of these patients reported a treatment effect. In Study 408 there were five patients, all pre-treated with botulinum toxin, who became positive for neutralising antibodies during the

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study, but all of the patients still reported a treatment effect. The study durations were too short to adequately assess antibody development or its clinical consequences.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of Xeomin and Botox for the treatment of cervical dystonia, based on claims of similar clinical efficacy, safety and unit dosing, as demonstrated in the results of the Benecke study. Xeomin is priced lower (\$330) than Botox (\$357) per 100 U vial. Where an equal number of vials of Xeomin or Botox are used, Xeomin will represent a cost savings.

Other Discussion Points:

- The Committee discussed that the short duration of the included trials does not permit adequate assessment of antibody development or patient response following repeated injections of Xeomin. Therefore there is insufficient evidence to support the claim that Xeomin is less immunogenic than Botox because it has less complexing proteins.
- Oral medication regimens are used second line to botulinum toxin as they may have adverse events associated with them and there is not good quality evidence for their effectiveness.
- Total TWSTRS scores and TWSTRS disability subscores were not reported in the Benecke study, which would have provided a more comprehensive overview of the impact of both Xeomin and Botox on cervical dystonia.
- The Committee noted that there is no evidence assessing the sequential use of botulinum products in patients where Botox has not provided the desired therapeutic effect as these patients were not included in the Xeomin trials. The Benecke study primarily provides information on whether or not patients already receiving Botox can switch to a similar Xeomin dose, but it does not provide information on the relative effectiveness of Xeomin and Botox in a treatment naïve population.
- 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.
- The Committee discussed that in clinical practice, clinicians may prefer to use low botulinum toxin A doses and longer treatment intervals when possible to minimize the development of neutralizing antibodies, which can potentially lead to treatment failure.

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.

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About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans.

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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