CEDAC FINAL RECOMMENDATION

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Xeomin be listed similar to the way drug plans currently list Botox for blepharospasm.

Reasons for the Recommendation:
1. The Committee considered that in the treatment of blepharospasm, 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 Jankovic Rating Scale, a measure of blepharospasm 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:
Patients included in the trials evaluating Xeomin in blepharospasm had a stable therapeutic response to botulinum toxin; therefore, there is no evidence that sequential use of Xeomin would be effective in individuals where Botox has not provided the desired therapeutic effect.

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 blepharospasm.

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.

Xeomin is given as an intramuscular injection and is available as a powder for reconstitution (100 units [U] per vial). The Health Canada recommended dose for Xeomin is 1.25 U to 2.5 U per injection site, initially; treatment of blepharospasm usually requires multiple injections per eye. The initial dose should not exceed 25 U per eye and subsequent total dosing should not exceed 70 U per treatment. The recommended interval between each treatment is at least 12 weeks.

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

Clinical Trials
The CDR systematic review included three double-blind RCTs in patients with blepharospasm. There was one placebo-controlled trial and two trials comparing Xeomin with Botox.

- The Roggenkamper study (N = 303) is a double-blind RCT that evaluated the non-inferiority of Xeomin compared with Botox. The effects of treatment were evaluated at three weeks and patients were followed up to 16 weeks or until another treatment was required.
- Study NCT00761592 (N = 65) is an unpublished trial that evaluated the superiority of Xeomin compared with Botox. The effects of treatment were evaluated at four weeks and patients were followed up to 14 weeks. After 11 weeks, patients had the option to request another treatment. Limited information was available for this study as it was not conducted by the manufacturer of Xeomin.
- Study 433 (N = 109) is an unpublished trial that evaluated the superiority of Xeomin compared with placebo. The effects of treatment were evaluated at six weeks and patients were followed up to 20 weeks or until a new treatment session was required.

All trials enrolled patients who had a stable therapeutic response when treated with Botox. The inclusion of only patients successfully pre-treated with Botox limits the generalizability of results to treatment-naïve patients or patients who have had an unsatisfactory therapeutic response to Botox, either initially or over time. Study doses of Xeomin and Botox were based on pre-trial Botox doses; in all trials, the total dose used was never greater than 100 U. In the Roggenkamper study and Study 433, concomitant medications not related to the treatment of blepharospasm were allowed and patients were allowed to continue on stable doses of any drugs to treat focal dystonias. Enrolled patients had moderate severity blepharospasm as indicated by baseline scores of scales measuring blepharospasm symptoms such as the Jankovic Rating Scale (JRS) and the Blepharospasm Severity of Disability Index (BSDI). 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 differed in the three trials. The primary outcome of the Roggenkamper trial was the JRS sum score at week three (non-inferiority margin of 0.8 points). The primary outcome of Study NCT00761592 was the change from baseline in the BSDI at week four. The primary outcome of Study 433, the placebo-controlled trial, was the change from baseline in the JRS severity subscore at week six.

- The JRS sum score quantifies the disease burden associated with blepharospasm and ranges from zero to eight with higher scores indicating greater disease burden. It is composed of two subscales: severity (ranging from zero to four) and frequency (ranging from zero to four). A two point change in the JRS sum score has been validated as being clinically meaningful.
- The BSDI measures functional outcomes with scores ranging from zero to four on each of six items (reading, driving a vehicle, watching television, shopping, doing everyday activities and walking) with higher scores indicating greater functional impairment. A 0.7 point change in the BSDI has been validated as being is clinically meaningful.

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

Results

Efficacy or Effectiveness

- Two of the included trials, Roggenkamper and Study NCT00761592, compared Xeomin with Botox. In the Roggenkamper study at week three, improvements in JRS sum score (primary outcome) were observed in both the Xeomin and Botox groups (-2.83 and -2.65, respectively) and Xeomin was demonstrated to be non-inferior to Botox (Δ = -0.23, 95% CI: -0.68 to 0.22). Improvements in BSDI scores and global efficacy assessments by patients and investigators were also similar between Xeomin and Botox patients. Non-significant differences between Xeomin and Botox were also observed in Study NCT00761592. Changes from baseline observed in the Roggenkamper study were clinically meaningful for both the Xeomin and Botox groups.
- In Study 433, there was a statistically significant improvement in JRS severity subscore at week six for Xeomin compared with placebo (Δ = -1.0, 95% CI: -1.4 to -0.6), which is also a clinically meaningful difference. Xeomin was also statistically significantly better than placebo for the JRS frequency subscore, JRS sum score, BSDI, and global efficacy assessments by patient and investigator.

Harms (Safety and Tolerability)

- The proportions of patients with a serious adverse event were low and similar between treatment groups in all three studies, ranging from zero to 3.2% across groups and trials. There were no withdrawals due to adverse events.
- The development of neutralizing antibodies was reported in Study 433 and in the Roggenkamper study. Two Xeomin patients and no Botox patients tested positive at the final study visit and both Xeomin patients had a treatment response. The study duration was too short to adequately assess antibody development or its clinical consequences.
- The proportions of patients reporting an adverse event was not statistically significantly different between treatment groups but rates were lower in the Roggenkamper study (27% to 29%) compared with the other studies (62% to 70% in Study 433 and 68% to 73% in Study NCT00761592).
- Botulinum toxin may diffuse to adjacent muscles, potentially causing paralysis and muscle weakness. Diffusion-related adverse events were not statistically significantly different between treatment groups in all studies, although, in Study 433, ptosis did occur in

statistically significantly more patients in the Xeomin group compared with placebo (18.9% versus 8.0%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of Xeomin and Botox for the treatment of blepharospasm, based on claims of similar clinical efficacy, safety and unit dosing, as demonstrated in the results of the Roggenkamper 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 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 the short duration of trials does not permit adequate assessment of antibody development or patient response following repeated injections of Xeomin; therefore, based on data from the included trials there is insufficient evidence to demonstrate that because Xeomin has less complexing proteins, it is less immunogenic than Botox.
- First line treatment for blepharospasm includes behavioural and environmental controls to minimize sensory input and irritations, following which guidelines support botulinum toxin as a treatment option.
- The Committee discussed that in clinical practice, clinicians may prefer to use low doses of botulinum toxin A and longer injection 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.

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.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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