CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

incobotulinumtoxinA
(Xeomin)
(Merz Pharmaceuticals GMBH)

Indication : Chronic sialorrhea associated with neurological disorders

August 26, 2021

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0678
Name of the drug and Indication(s)	Xeomin (IncobotulinumtoxinA) for the treatment of chronic sialorrhea associated with neurological disorders in adults transfusions
Organization Providing Feedback	FWG

1. Recommendation revisions

Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.

Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions

Complete this section if major or minor revisions are requested

N/A

3. Clarity of the recommendation

Complete this section if editorial revisions are requested for the following elements

a) Recommendation rationale

N/A

b) Reimbursement conditions and related reasons

Drug Plans suggest:

1. Adding ‘The maximum duration of initial authorization is 16 weeks.’ to the initiation criteria, and removing this from the renewal criteria.
2. Removing from the renewal criteria ‘Subsequent authorizations following the initial authorization are for a one year period.’
3. Renewal criteria should include a statement such as Reimbursement of incobotulinumtoxinA should be renewed in patients who have exhibited a reduction in the severity and/or frequency of sialorrhea compared to baseline.

Discontinuation criteria then becomes: Subsequent reimbursement should be discontinued if the treatment effect compared to the previous cycle is not maintained.

c) Implementation guidance
N/A

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Xeomin
Indication(s)	Sialorrhea
Organization	Parkinson Québec
Contact information[a]	Name: [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

La communauté Parkinson du Québec se réjouit de votre recommandation positive concernant le remboursement de Xeomin® pour le traitement de la sialorrhée chez les patients atteints de troubles neurologiques.

Notre enquête de terrain auprès des personnes qui vivent avec la maladie de Parkinson et de leurs proches aidants démontre le poids du fardeau de ce symptôme. Celui-ci, trop souvent sous-estimé, a un impact majeur sur la vie personnelle et sociale de cette population.

La sialorrhée chronique est un symptôme qui se développe tard chez les parkinsoniens, la plupart du temps quand ceux-ci ne sont plus couverts par un régime d'assurance privé. Nous apprécions votre recommandation quant à la réduction de 30% du prix proposé par le fabriquant. Nous sommes toutefois inquiets que les négociations provinciales à cette hauteur de prix n'aboutissent pas au traitement du plus grand nombre.

Au nom de toute la communauté Parkinson du Québec, nous vous remercions de votre travail indépendant de revue qui est indispensable à l'utilisation optimale des médicaments et des dispositifs médicaux.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

If not, what aspects are missing from the draft recommendation?

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Parkinson Québec*
Position	*Romain Rigal, Director Programs and Services*
Date	*28/08/2021*
☐	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Merz Pharma (Unconditional educational grant (K30$) received 3 months after feedback was submitted to CADTH	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0678-000
Brand name (generic)	XEOMIN (incobotulinumtoxinA)
Indication(s)	For the treatment of chronic sialorrhea associated with neurological disorders in adults.
Organization	Merz Therapeutics, a business of Merz Pharma Canada Ltd.
Contact information[a]	Name: [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Merz Therapeutics (Merz) agrees with CDEC's draft recommendation of XEOMIN for the treatment of chronic sialorrhea associated with neurological disorders in adults, if the reimbursement conditions are met.

Clinical Feedback

Patients identified continued unmet need for a treatment that manages the frequency and severity of sialorrhea with mild or adverse effects (*Rationale for the Recommendation,* page 2; *Stakeholder Perspectives, Patient Input,* page 5). Merz agrees with CDEC's assessment that the results of the SIAXI trial demonstrate that Xeomin may address these needs (*Rationale for the Recommendation,* page 2). Merz further agrees with CADTH's appraisal of SIAXI as a rigorously designed trial with no major risks of bias (*Clinical Evidence, Critical Appraisal,* page 8), and the opinion of the clinical expert consulted by CADTH that the results observed with Xeomin for the patient's global impression of change and reduction in drooling severity and frequency were clinically meaningful (*Clinical Evidence, Efficacy Results,* page 8).

SIAXI was a multicenter, double-blind randomized controlled trial with a large sample size representative of the patient population in Canadian clinical practice.[1] The efficacy and safety of Xeomin for the treatment of chronic sialorrhea associated with neurological disorders in adults have therefore been demonstrated by robust, Grade A clinical evidence. XEOMIN is the only approved treatment for chronic sialorrhea associated with neurological disorders in adults in Canada. Its reimbursement will provide equitable and evidence-based access to treatment for patients with debilitating and troublesome sialorrhea.

Economic Feedback

Merz would like to note that CADTH's reanalyses of the cost-effectiveness of Xeomin should be interpreted with caution, given the uncertainty associated with key assumptions. Merz is appreciative of CADTH's consideration of a scenario analysis of the cost-utility model in which Xeomin and Botox (onabotulinumtoxinA) are equally effective, the results of which suggested that Xeomin is less costly than Botox at the currently available prices (*Economic Evidence, Budget Impact,* page 11).

The results of CADTH's reanalysis of the budget impact of Xeomin for this indication should be interpreted with caution. The higher end of CADTH's sensitivity analyses on the budget impact analysis

assuming that the prevalence of sialorrhea used in the model applies to all of those with neurological conditions, not just those with severe disease (*Economic Evidence, Budget Impact,* page 11) are unlikely to occur, given that the evidence demonstrates that only a subset of patients with neurological conditions experience sialorrhea[2–4], and the likelihood of experiencing sialorrhea increases with increasing severity of the underlying neurological condition.[3,5,6]

References

1. Jost WH, Friedman A, Michel O, et al. SIAXI: Placebo-controlled, randomized, double-blind study of incobotulinumtoxinA for sialorrhea. *Neurology*. 2019;92(17):e1982-e1991. doi:10.1212/WNL.0000000000007368

2. Morgante F, Bavikatte G, Anwar F, Mohamed B. The burden of sialorrhoea in chronic neurological conditions: current treatment options and the role of incobotulinumtoxinA (Xeomin®). *Therapeutic Advances in Neurological Disorders*. 2019;12:1756286419888601. doi:10.1177/1756286419888601

3. Kalf JG, de Swart BJM, Borm GF, Bloem BR, Munneke M. Prevalence and definition of drooling in Parkinson's disease: a systematic review. *J Neurol*. 2009;256(9):1391-1396. doi:10.1007/s00415-009-5098-2

4. Møller E, Karlsborg M, Bardow A, Lykkeaa J, Nissen FH, Bakke M. Treatment of severe drooling with botulinum toxin in amyotrophic lateral sclerosis and Parkinson's disease: efficacy and possible mechanisms. *Acta Odontologica Scandinavica*. 2011;69(3):151-157. doi:10.3109/00016357.2010.545035

5. Fasano A, Visanji NP, Liu LWC, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol*. 2015;14(6):625-639. doi:10.1016/S1474-4422(15)00007-1

6. Nóbrega AC, Rodrigues B, Melo A. Is silent aspiration a risk factor for respiratory infection in Parkinson's disease patients? *Parkinsonism Relat Disord*. 2008;14(8):646-648. doi:10.1016/j.parkreldis.2007.12.007

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐

N/A

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

Merz agrees with the rationale for the recommendation: that there is an unmet need for a treatment that manages the frequency and severity of sialorrhea with mild or rare adverse effects and that Xeomin is a treatment that can address this unmet need based on the results of the SIAXI trial (*Rationale for the Recommendation,* page 2).

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

Merz acknowledges the key issues related to implementation identified by drug programs (*Stakeholder Perspectives, Drug Program Input,* page 6) and agrees with the responses from the clinical expert consulted by CADTH for the review. Moreover, Merz is aligned with the implementation guidance provided by CDEC in the recommendation (*Implementation Guidance,* page 4) as it is appropriate, evidence-based, and aligned with the Health Canada indication and approved dosing.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

The reimbursement conditions for initiation, renewal, discontinuation, and prescribing identified by CDEC (*Table 1. Reimbursement Conditions and Reasons* page 3) are clearly grounded in the clinical evidence and aligned with input from practicing clinicians in Canada. As such, Merz agrees that they are appropriate.

Merz would like to note that the ICER resulting from CADTH's reanalysis is associated with some uncertainty. The submitted results of the cost-utility analysis indicated that Xeomin was cost-effective at a willingness to pay threshold of $50,000 per QALY, with an ICER of $14,417 per QALY gained for Xeomin + standard of care (SoC) compared to SoC alone (*Table 2: Summary of Economic Evidence,* page 10).

[a] CADTH may contact this person if comments require clarification.