CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

immune globulin human and recombinant human hyaluronidase (HyQvia)

(Takeda Canada Inc.)

Indication: Humoral immunodeficiency

February 10, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**ST0695**
Brand name (generic)	HyQvia (Normal Immunoglobulin (Human) 10% and Recombinant Human Hyaluronidase)
Indication(s)	As replacement therapy for primary humoral immunodeficiency and secondary humoral immunodeficiency in adult and pediatric patients two years of age and older.
Organization	Clinical Immunology Network-Canada (CINC)
Contact information[a]	Name: Luis Murguia-Favela. CINC-Chair

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.

- "In the absence of a control group, there is substantial uncertainty associated with inferring causality associated with outcomes reported and, consequently, the relative safety and efficacy of IgHy10"
    - In the setting of rare diseases, such as primary immunodeficiencies, it is very challenging and many times impossible to run randomized, controlled trials. In addition, specifically for humoral deficiencies, the vast majority of the evidence we have on IVIG and SCIG products comes from prospective, open-label, non-randomized, non-controlled studies, such as the ones done for IgHy10. And beyond that, from post-hoc analyses and "real world' experience with these treatments. We believe that the safety of IgHy10 has been sufficiently shown in the studies and the post-hoc analyses.
- "high discontinuation rates" "only a small portion of patient was able to administer IgHy10 at home"
    - Again, the number of patients in the IgHy10 is relatively small but comparable to all other trials for immunoglobulin replacement therapies. Post-hoc analyses and real world experience with availability of IgHy10 in various countries has shown us that this treatment has been well tolerated by patients at home.
- "no evidence was identified that compared the efficacy or safety of IgHy10 with other immunoglobulin replacement therapies"
    - There is a recent post-hoc analysis evaluating the efficacy of IgHy10 compared to that of IVIG and SCIG and it is very similar. Wasserman RL, et al. *Immunotherapy*. Dec 2021;14(2).
- As clinicians specialized in treating patients with primary and secondary humoral immunodeficiencies, we continue to believe that IgHy10 is a valuable treatment option for all patients needing Ig replacement therapy and especially for those subgroups of patients that we mentioned in our original feedback submission. We also believe that, with proper administration training, the majority of patients would be able to administer this treatment at home.

Expert committee consideration of the stakeholder input		
	Yes	☒

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

The section in the recommendation summarizing our feedback was very brief and most of what we had expressed was actually mentioned in the section referring to the 2 additional specialists consulted by CADTH. This may, of course, represent clear agreement among all clinicians that provided input that IgHy10 is a valuable treatment option to have in Canada for our patients.

With regards to the slight difference in the recommendation for assessment of treatment response we mentioned that it should happen at least every 6 to 12 months; however, we certainly agree that more frequent assessment (3 to 6 months as suggested by the additional specialists consulted) would be ideal, whenever possible.

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.
N/A

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.
N/A

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

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		
1. 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.		
2. 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		
3. 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: • Luis Murguia-Favela, MD FRCPC on behalf of CINC		

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0695
Name of the drug and Indication(s)	Normal Immunoglobulin (Human) 10% and Recombinant Human Hyaluronidase (HyQvia) as replacement therapy for primary humoral immunodeficiency and secondary humoral immunodeficiency in adult patients
Organization Providing Feedback	FWG – Canadian Blood Services

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	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0695-000
Brand name (generic)	immune globulin human and recombinant human hyaluronidase
Indication(s)	Humoral immunodeficiency
Organization	Canadian Immunodeficiencies Patient Organization (CIPO) and CIPO Medical Science Advisory Committee
Contact information[a]	Name: Whitney Ayoub Goulstone and Dr. Stephen Betschel

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

We disagree with the recommendation to not reimburse *IgHy10*. It is our opinion that given the input from multiple stakeholders including clinicians, patients and experts, CADTH was given reasons (illustrated below) to provide a favourable recommendation.

From the Rationale for the Recommendation, p.3, *"In the absence of a control group, there is substantial uncertainty associated with inferring causality associated with outcomes reported and, consequently, the relative safety and efficacy of IgHy10"*

- **Response**: In this case, primary immunodeficiency patients were part of the studies in question. There cannot be a control group when patients are using a treatment that cannot be disrupted, "*Patients with Primary Immunodeficiency are completely dependent on IG for survival*" (Protecting Access to Immune Globulins for Canadians, 2018, Health Canada). Patients with primary immunodeficiency are unlikely to stop treatment or the possibility of stopping treatment (taking a placebo) to take part in a trial. Additionally, it would be considered by most, if not all research ethics boards, as unethical to stop treatment for a clinical trial. It is therefore our opinion that the CADTH review process may not appreciate this when dealing with rare diseases, especially those involving plasma protein products. To deny access to this product since certain trial criteria cannot be followed is both punitive and unfair to the immunodeficiency population.
- With respect to safety, this product has been available to primary immunodeficiency patients in 26 countries for over 8 years with no significant safety signals identified. It has also passed Health Canada review when obtaining NOC which considered safety of the product. Also, there is precedent for hyaluronidase in other injectables which have been widely used including Rituximab.
- It is also important to recognize that the trial design for this product was very similar to all the currently licensed and available SCIG and IVIG products currently in Canada. The clinical trials were designed in this manner due to the requirement that they adhere to ethical considerations when evaluating such products in the immunodeficiency patient population.

From the Discussion points, p.4: "*Clinical experts noted to CPEC that the rate and proportion of patients reporting systemic adverse events (AEs) with IgHy10 was higher than what is observed with cSCIg in clinical practice"*

- Response: Clinician experts, clinician input and patient input all indicated that the primary group likely to qualify for this treatment first would be patients switching from IVIG to IgHy10. IVIG has a very high rate of AEs, however this was not noted or taken into account. The

pressures on the IVIG clinics, bedspace and administrative costs at the hospital level were not discussed, nor is it known if the possible cost-savings to the healthcare system from patients switching from IVIG to IgHy10 were taken into account. From the Clinical input p.5: "*The clinical experts also indicated that patients who are expected to benefit most from switching from IVIg to treatment with IgHy10 include patients with certain comorbidities, those with limited access to health care facilities, those who had severe adverse effects to IVIg, have difficult venous access, or those who prefer not to miss school/work to receive treatment".*

- From CIPO patient submission: "*Patients requiring IVIG therapy, either due to lack of other treatment options or due to failure on SCIG therapy, typically require one day per month to be allocated to treatment and recovery, as treatment requires travel to a designated infusion clinic, significant time for the infusion and significant time for recovery (as fatigue is a common side-effect of IVIG). Many individuals with PI have difficulty accommodating a full day per month for IVIG treatment while meeting the requirements of their employment."*
- From the Clinical Input submission: "*This preparation allows for doing the frequency of the intravenous route of treatment administration (once a month) while maintaining the benefits of the subcutaneous route of administration: less systemic side effects, convenience, and medical cost savings due to at-home treatment delivery."* While the report noted on pg. 6, "*The clinician groups also noted that there are considerable benefits associated with the ability to treat patients at home, particularly in terms of rising capacity issues for both inpatient and outpatient beds and the increasing costs of medicines"* the clinician submission also noted that it is important to keep primary immunodeficiency patients out of the hospital, "*Patients with primary immunodeficiency encounter a unique conundrum with respect to receiving (IVIG) treatment at a hospital. As their disease makes them uniquely susceptible to pathogens, the requirement to attend an infusion clinic at a hospital brings with it the risk of hospital-acquired infections."*

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	☒

It is the opinion of the Canadian Immunodeficiencies Patient Organization (CIPO), that the draft recommendation demonstrates that our stakeholder input was not taken into consideration. This is shown by the lack of any reference to the patient submission outside of the three paragraphs (14 lines of text) under "Patient Input" on pg 4. Many of the conclusions reached in our submission were ignored, example:

- From CIPO patient submission, "*There is clearly a population of PI patients that would derive great benefit from a therapy that can be administered at home while affording the same dosing frequency as intravenous immunoglobulin (IVIG) treatments (enabling high-dose infusions every 3–4 week) along with the benefit of reducing the number of infusion sites and adverse events (compared to IVIG therapies).*
- Of the 14 lines of text the patient submission was afforded in review, 3 (21.5%) were given to the following as a conclusion of the section: p.4 CADTH review "*Telephone interview respondents indicated a curiosity about trying IgHy10, but also described a desire for the same result from treatment, concerns about having a negative experience due to switching therapies, and whether IgHy10 it would be an appropriate treatment option for the individual patient seeking treatment."* We find this to be misleading. We had 246 respondents take part in our survey and only 8 telephone interviews, we do not feel it appropriate for CADTH to make this generalization. In our survey, over 60% (132) of respondents said it was **very important** for them to have access to new therapies for primary immunodeficiency and a further 18.72% (41) said it was **important**. The numbers that represent over 78% of our respondents were omitted.

We believe not only should our survey be more closely considered, but it should also be more heavily weighted. Only patients and caregivers understand the burden of illness and the entirety of the socio-economic impact.

Clarity of the draft recommendation

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

Yes, the reasoning is clearly stated, however we disagree with the recommendations and the reasoning used in some ways as described.

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

Yes, but we disagree with some of the key findings stated. From the review: "*Training costs for IgHy10 were not incorporated as part of the cost-minimization analysis and likely underestimated relevant costs under the public healthcare payer perspective."*

- Response: There is no need to, as the manufacturer would assume all training costs. Patient support programs assume all costs regarding patient and nurse training. It is usual for plasma products used in home for the manufacturer's patient support program to implement additional training supports necessary as to nursing support in home on an ongoing basis until the new patient feels comfortable to infuse on their own.

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

CADTH has made the recommendation to not reimburse. The rationale for this decision is outlined in the decision, however, we disagree with the following key limitations as noted in the report:

- *Market share distributions should not be used to aggregate and average costs of IVIG and SCIG comparators in a CMA. Further, these market share may not reflect the distribution of these treatments for the indicated populations.*
    - Revising the market share to reflect the new drug scenario is an interesting concept but we fail to see how this would affect this product. In the current distribution landscape, this product would be viewed as a product that falls under Canadian Blood Services formulary, which is currently starting a RFP for plasma protein products and IGs for 2023. Market share absolutely does reflect the distribution of these treatments for PID and SID patients. CIPO would prefer if the decision was based on patient preference, however, market share does dictate which treatment is first, second, etc.
- *Patients with PID and SID were assumed to have differing doses; further, the use of a lower dose for each IVIG and SCIG product did not align with the dose typically used in Canadian clinical practice, and likely underestimated drug cost calculations.* While we will not comment on drug cost calculations (as we feel as a patient organization, this is not our area), we can comment on dosing guidelines in Canada. As per Canadian guidelines for primary immunodeficiency for both IVIG and SCIG dosing guidelines are below:
    - Typical dose in IVIG (0.4-0.6g/kg month)
    - Typical dose in SCIG (0.1-0.4g/kg week)

According to CIPO's Medical Science Advisory Committee the dosing for PI and SID are the same.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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A. Patient Group Information	
Name	Whitney Ayoub Goulstone
Position	Executive Director
Date	(08-02-2022)
☒	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**
CSL Behring	☐	☐	☒	☐
Grifols	☐	☐	☐	☒
Takeda	☐	☐	☐	☒

CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

immune globulin human and recombinant human hyaluronidase (HyQvia)

(Takeda Canada Inc.)

Indication: Humoral immunodeficiency

June 3, 2022

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

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Organization Providing Feedback	FWG

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No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☑
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification. **First paragraph, last three sentences** “The available evidence… most patients tolerate IgHy10.” Please mention here low numbers of patients who were able to self administer in the clinical trial. It would make the summary more balanced from evidence perspective.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. Requesting removal of following bullet from “discussion points”

• CPEC discussed that each province or territory will likely have different approaches to IgRT utilization management; therefore, renewal criteria should align with the jurisdictional guidelines. If CBS list it under the Named-Patient Contract program, then we can define the renewal criteria. If general benefit, then both initiation and renewal will be as per the province. Therefore, we would not want to draw attention to the fact that there are currently different access criteria for IgRT. If removal of the entire bullet is not possible, we recommend reducing the sentence to, "CPEC discussed that each province or territory will likely have different approaches to IgRT utilization management."
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

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3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.