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Reimbursement Recommendation

Teprotumumab (Tepezza)

Indication: In adults for the treatment of moderate to severe active thyroid eye disease (TED)

Sponsor: Amgen Canada Inc.

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Tepezza?

Canada's Drug Agency (CDA-AMC) recommends that Tepezza should not be reimbursed by public drug plans for the treatment of moderate to severe active thyroid eye disease (TED) in adult patients.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 3 randomized controlled trials (RCTs) in patients with moderate to severe active TED demonstrated that Tepezza improved proptosis and overall response at 24 weeks compared with placebo; however, vision outcomes, identified by patients and clinicians as a key treatment priority, were not assessed. Furthermore, the evidence regarding diplopia, another outcome of importance to patients and clinicians, had several limitations, including the use of subjective assessment methods, failure to meet multiplicity hierarchy testing, and uncertainty in the effect estimates due to wide confidence intervals (CIs).
- There was no direct comparative evidence evaluating the effectiveness of Tepezza versus any active treatment. The sponsor-submitted indirect evidence was insufficient to support a definitive conclusion about the comparative effects of Tepezza due to substantial limitations, including heterogeneity across included trials, reliance on unanchored matching-adjusted indirect comparisons (MAICs), failure to account for relevant effect modifiers, small effective sample sizes after matching, and considerable uncertainty in the effect estimates due to wide CIs. The indirect treatment comparison (ITC) evaluated Tepezza versus IV methylprednisolone (IVMP) only and did not include other relevant comparators such as rituximab, tocilizumab, and mycophenolate mofetil (MMF).
- The Canadian Drug Expert Committee (CDEC) acknowledged that moderate to severe active TED is a rare and serious condition associated with significant unmet clinical need. However, based on the evidence provided, the committee was unable to conclude that Tepezza addresses these unmet needs as effectively as, or more effectively than, existing off-label treatments. In addition, unlike current off-label drugs for this condition, evidence on the long-term effects of Tepezza remains limited.

Summary

Additional Information

What Is Moderate to Severe Active TED?

TED is an autoimmune disease that causes inflammation and expansion of muscle tissues around the eyes, leading to redness, swelling, pain, double vision, and eye bulging that can significantly affect quality of life. Moderate to severe active TED refers to a stage of TED characterized by clinically significant inflammation and tissue expansion around the eyes that causes functional impairment and visible eye changes and is ongoing (active) rather than stable. Moderate to severe active TED is a rare disease with an estimated prevalence of no greater than 5 in 100,000.

Unmet Needs in TED

There is a need for new treatments that address the underlying disease process of TED, relieve the symptoms (such as swelling, pain, redness, double vision, and bulging eyes), reduce side effects, and lead to reversal of the condition.

How Much Does Tepezza Cost?

Treatment with Tepezza is expected to cost approximately $215,175 per patient per 24-week treatment course, based on a patient weight of 73 kg.

Recommendation

CDEC recommends that teprotumumab not be reimbursed for the treatment of adult patients with moderate to severe active TED.

Rationale for the Recommendation

Evidence from 3 multicentre, double-masked, RCTs (TED01RV [N = 87], TEP-301 [N = 83], and TEP-303 [N = 54]) in patients with moderate to severe active TED demonstrated that treatment with teprotumumab results in improvements in proptosis and overall response at 24 weeks compared to treatment with placebo. However, CDEC noted that vision outcomes, identified by clinicians and patients to be of key importance, were not assessed. CDEC also observed that the trials used subjective methods for evaluating diplopia (another important outcome identified by patients and clinicians), the analysis for this outcome failed multiplicity hierarchy testing, and there was imprecision in the effect estimate due to large CIs.

CDEC acknowledged the clinical expert's observation that 1 of the main goals of therapy is reducing inflammation and that current off-label treatments in Canada (e.g., IVMP, rituximab, tocilizumab, and MMF) achieve that goal in many patients. Therefore, CDEC considered it necessary to compare teprotumumab to the currently available treatment to assess its comparative clinical effects. However, the reviewed trials had no direct comparisons to any of the drugs considered as relevant comparators. The sponsor submitted 2 ITCs of teprotumumab versus IVMP using unanchored MAICs to assess proptosis and diplopia responses and health-related quality of life (HRQoL) in patients with active TED. CDEC noted that the sponsor-submitted ITCs had significant limitations, including analyses based on an unanchored MAIC. Other limitations include not considering relevant prognostic variables (e.g., vision, disease duration, gaze-evoked orbital pain) and effect modifiers in the analyses, small effective sizes after matching, and methodological heterogeneity across IVMP trials (e.g., baseline characteristics, study designs). In addition, the comparisons were restricted to IVMP only, without considering other drugs (e.g., rituximab, tocilizumab) that are used off-label but are relevant comparators in Canada. The results of the ITCs suggest that teprotumumab was favoured over IVMP for changes in proptosis, diplopia, and HRQoL. However, interpretation of the findings is limited due to the large CIs around the effect estimates and significant limitations. Therefore, CDEC concluded that the evidence from both ITCs was insufficient to determine the comparative clinical effect of teprotumumab versus IVMP.

During the reconsideration meeting, CDEC noted that the sponsor acknowledged uncertainty in the evidence from the submitted ITC and RCTs regarding the comparative clinical effectiveness of teprotumumab versus current off-label treatments used in Canada. The committee agreed that moderate to severe active TED is a rare and serious condition associated with significant unmet clinical need, as identified by input from patient groups and clinician groups. However, CDEC was unable to conclude that teprotumumab addresses these unmet needs as effectively as or more effectively than existing off-label treatments based on the evidence provided. In addition, and unlike current drugs used off-label for this condition, evidence on the long-term effects of teprotumumab remains limited.

Discussion Points

- **Reconsideration Request:** The sponsor requested a major reconsideration of the initial draft recommendation to not reimburse teprotumumab for patients with moderate to severe active TED. There were 5 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The sponsor was of the opinion that CDEC's initial assessment did not adequately reflect the rarity or severity of moderate to severe active TED and did not consider the disease-modifying mechanism of teprotumumab compared with existing off-label treatments, which they characterized as immunosuppressants that do not modify the core pathophysiology of the disease. The sponsor asserted that, despite points of uncertainty in the RCT and ITC evidence, they represent the highest-quality data currently available on TED and indicate that teprotumumab provides superior or comparable clinical value relative to current standard treatments such as IVMP. The sponsor submitted new safety and HRQoL evidence intended to address the lack of comparative safety and HRQoL data that CDEC identified in its initial assessment. The sponsor also claimed that the initial recommendation reflected a generalizability concern raised by consulted clinical experts, which they argued was not representative of input provided by patient or clinician groups.
- **Unmet Needs:** During the initial meeting, CDEC discussed unmet needs identified by patients (avoiding adverse events [AEs] associated with steroid use) and clinical experts (addressing incomplete remission with existing therapies in some patients). CDEC also discussed treatment options for people with tuberculosis or liver failure, reduced side effects, and disease reversal, as well as important outcomes such as improvement in signs and symptoms (less swelling, less eye pain, reduced redness, no sensitivity to light). The committee acknowledged that treatment with teprotumumab results in statistically significant improvements in proptosis and overall response compared to placebo. However, CDEC noted there is insufficient evidence to suggest whether teprotumumab is similar to or better than the current therapies used in Canada in improving proptosis and overall response in patients with active TED. The committee also discussed the clinical experts' input, which indicated that although proptosis is an important outcome that impacts the quality of life of some patients, the functional goal of treatment is comfort, reduction in inflammation with preservation of vision, and avoidance of diplopia. Moreover, CDEC noted that the reviewed clinical trials lack evidence to suggest that teprotumumab could improve HRQoL compared to existing therapies.
- **Rarity or Severity of Moderate to Severe Active TED:** During the reconsideration meeting, CDEC discussed the sponsor's view that the committee insufficiently considered the rarity or severity of moderate to severe active TED, and therefore inadequately applied the unmet clinical need domain within its deliberative framework. CDEC acknowledged that, while the discussion section of the initial recommendation did not stress the rarity and severity of the condition, this was recognized in the draft recommendation, as stated in the second paragraph of the Background section. The committee noted further that the rarity and severity of moderate to severe active TED was reflected in the CDA-AMC clinical review report, which served as the primary evidence base for its deliberations. Also, the committee acknowledged that the guidelines, published references, and input received from interest

groups included in the clinical review all characterize moderate to severe active TED as a rare and serious disease. However, CDEC emphasized that the initial draft recommendation was based on the totality of evidence and multiple deliberative considerations, of which the rarity and severity of moderate to severe active TED represented 1 component.

- **Teprotumumab as a Disease-Modifying Therapy:** During the reconsideration meeting, CDEC also discussed the sponsor's claim that teprotumumab is the only disease-modifying therapy for TED and is distinct from existing off-label treatments, which the sponsor characterized as simply broad immunosuppressants that do not modify the core pathophysiology of moderate to severe active TED. The committee emphasized that the disease-modifying ability of teprotumumab was deliberated during the initial meeting, at which it was determined that the reimbursement review process evaluates interventions based on their effects on clinically meaningful outcomes and does not directly assess disease-modifying properties. CDEC noted further that the sponsor did not provide conclusive evidence demonstrating that the disease-modifying mechanism of teprotumumab translates into improved outcomes of importance to clinicians and patients compared with existing off-label treatments.
- **Adverse Effects:** Patients emphasized the need for reduced adverse effects caused by treatments for TED. During the initial meeting, CDEC noted that, based on the evidence from the clinical trials, teprotumumab likely increases notable harms (i.e., hyperglycemia and hearing impairment) compared to placebo. CDEC also acknowledged the clinical experts' input on the emerging real-world evidence around ototoxicity and the need for more data to assess the durability of hearing impairments and the long-term safety of teprotumumab.
- **New Cohort Study Evidence:** During the reconsideration meeting, CDEC reviewed evidence from a population-based cohort study submitted by the sponsor in support of their reconsideration request. The study compared the long-term safety outcomes of teprotumumab versus oral or IV glucocorticoids, focusing on hearing loss as well as renal and cardiovascular AEs. CDEC noted that, although the evidence appeared to corroborate the increased risk of hearing loss with teprotumumab observed in clinical trials, it was inconclusive on the effects on the risk of renal or cardiovascular AEs. However, the committee determined that overall, substantial uncertainty due to methodological limitations of the study precluded drawing a definitive conclusion from its findings.
- **HRQoL:** During the initial meeting, CDEC noted that patients and clinicians highlighted improvement in HRQoL as an important outcome of treatment for patients with TED. CDEC observed that, although an improvement in disease-specific HRQoL outcomes (Graves ophthalmopathy quality-of-life questionnaire [GO-QoL] appearance and visual functioning subscales) was reported in the clinical trials, a firm conclusion could not be drawn regarding the clinical meaningfulness of the observed effect due to lack of precision and failed multiplicity hierarchy testing.
- **HRQoL From the Unanchored MAIC:** During the reconsideration meeting, CDEC reviewed evidence from an unanchored MAIC submitted by the sponsor in support of their reconsideration request. The analysis indirectly compared HRQoL outcomes for teprotumumab versus IVMP in patients with active TED. CDEC noted that, although the results suggested that treatment with

teprotumumab may be favoured over IVMP in improving HRQoL outcomes, the findings were associated with significant uncertainty due to key methodological limitations. These included the unanchored design, heterogeneity across the IVMP studies, reduced effective sample size following matching, and inability to adjust for relevant prognostic factors or assess potential effect modifiers. The committee concluded that the level of uncertainty in the evidence precluded drawing a definitive conclusion about the comparative effects of teprotumumab versus IVMP on HRQoL outcomes.

- **Uncertainty in Long-Term Efficacy:** During the initial meeting, CDEC also considered results from the long-term follow-up periods of the TED01RV and TEP-301 trials and the open-label extension (OLE) of the TEP-301 trial, which suggested a high relapse rate among patients whose proptosis had responded previously and a lack of sustained responses after treatment. However, CDEC also noted that the trials' long-term follow-up and OLE phases involved small sample sizes. Therefore, CDEC concluded that the evidence from these extension studies was insufficient for a decisive conclusion about the long-term effects of teprotumumab for patients with TED.
- **Generalizability:** During the initial meeting, CDEC acknowledged the clinical experts' input that if teprotumumab were to be prescribed, it would be for patients who have already tried the drugs currently used in Canada for active TED and whose disease has not responded adequately. However, all 3 clinical trials excluded patients who were using other active TED treatments, without information on how their disease responded to those therapies. Therefore, it was unclear if the observed effects of teprotumumab would be replicated in the population for whom the drug may be considered within the clinical setting in Canada.
- **Interpretation of Generalizability Concerns and Place in Therapy:** During the reconsideration meeting, CDEC discussed the sponsor’s claim that the initial draft recommendation raised concerns about generalizability based on input from clinical experts consulted by CDA-AMC, whereas patient and clinician groups did not express such concerns. CDEC noted input from the CDA-AMC reviewers indicating that the sponsor had raised the same issue during their review of the draft clinical review report and that it had been addressed at that stage without objection from the sponsor. Specifically, the reviewers explained that the sponsor’s claim relied on a selective interpretation of a single sentence within a paragraph summarizing the clinical experts’ views on the generalizability of multiple aspects of the sponsor’s clinical studies. CDEC noted that focusing on that sentence in isolation did not reflect the overall interpretation of generalizability presented by the consulted experts. CDEC determined that the underlying issue was about differing perspectives on the absence of vision preservation as a key outcome and the lack of data on outcomes in patients using other active TED treatments who were excluded from the teprotumumab studies. The committee noted that the absence of data on outcomes in patients using other active TED treatments contributed to differing views on the appropriate place in therapy of teprotumumab in moderate to severe active TED. Therefore, some clinicians, including the consulted clinical experts, indicated that teprotumumab should be used as a second-line therapy following inadequate response to treatments currently used off-label, whereas others favoured its use as a first-line option. CDEC noted that the sponsor did not provide any evidence to consistently clarify the place in therapy of teprotumumab.

- **Equity of Access:** During the initial meeting, CDEC discussed ethical and equity considerations in attaining a timely TED diagnosis. While ophthalmology services are publicly insured across most provinces and territories, patients without private insurance may face barriers earlier in the diagnostic pathway — particularly when access to optometrists, who often serve as gatekeepers to ophthalmologic care, is not publicly covered. These access challenges may contribute to delays in diagnosis and treatment, with disproportionate impacts on individuals with limited financial resources.

Background

TED (also known as Graves ophthalmopathy or orbitopathy, dysthyroid eye disease, or thyroid-associated orbitopathy) is a serious autoimmune disease that is associated with Graves or Basedow autoimmune thyroid disease. The TED pathogenesis is driven by inflammation that is caused by autoantibodies targeting IGF-1R on fibroblasts in and around the orbital cavity (eye socket). This inflammation causes expansion of muscle tissues and fat, which leads to orbital swelling, pain, proptosis, diplopia (double vision), and potentially vision-threatening compression of the optic nerve (dysthyroid optic neuropathy). Older age, male sex, tobacco use, radioiodine therapy, and high levels of thyroid-stimulating hormone receptor antibodies are considered risk factors for TED.

The estimated incidence of TED is 4.83 cases per 100,000 population, and the prevalence of TED is 89.7 cases per 100,000 population, with 94.82% of TED cases involving adult patients (≥ 18 years). There is no disease marker for TED. The evaluation of a patient with TED can include laboratory assessments (thyroid-stimulating hormone receptor antibody, free T4, total T3), examination of the eyes, assessment of disease activity (clinical activity score [CAS] and vision, inflammation, strabismus, and appearance assessments) and severity, and imaging (CT scans, MRI).

The natural course of TED varies but progresses along a continuum of 2 phases: an active inflammatory phase (CAS ≥ 3 points) and a chronic phase (CAS 0 or 1; that is, little or no inflammation). Active TED involves progressive inflammation and orbital tissue expansion that rapidly progresses to maximal disease severity (based on signs and symptoms) and fibrotic changes in the orbit. After inflammation has ameliorated, TED progresses to a chronic stage with persistent structural and appearance changes (due to underlying fibrosis). Severity of TED is broadly categorized by the European Group on Graves' Orbitopathy (EUGOGO) as mild (minor impacts on daily life that do not warrant immunosuppression or surgery), moderate to severe (TED that does not currently threaten vision but sufficiently impacts the patient's life to justify intervention), or sight-threatening (dysthyroid optic neuropathy, corneal breakdown, and/or globe subluxation). HRQoL is severely impacted in both the active and chronic phases, which is due to pain, proptosis, and diplopia as key manifestations, as well as the potential need for surgical procedures to correct the structural and appearance changes caused by TED.

Several options for pharmaceutical management are available for moderate to severe active TED, as per the published EUGOGO guidance from 2021 and the American Thyroid Association and European Thyroid Association guidelines from 2022. According to the experts consulted by CDA-AMC, current treatments

for active TED include IVMP and orbital radiation, IVMP and MMF, rituximab, and tocilizumab. IVMP, MMF, rituximab, and tocilizumab are used off-label in Canada. The experts further highlighted that glucocorticoids are the traditional main choice of therapy and that they can be combined with radiotherapy, although with the risk of retinopathy and cataracts. The experts also reported that statins appear to have some benefit with glucocorticoids but are likely underused. Surgery is considered effective for patients with active TED, with sight-threatening orbitopathy that is unresponsive to glucocorticoids.

Surgery is usually not performed until after the active phase of TED. However, in cases of acute optic nerve compression or corneal exposure, early surgery is performed. The experts reported that, for the correction of diplopia, strabismus surgery is required but is only an option once the orbit is stabilized. Nonsurgical options for large-angle diplopia include Fresnel prisms, translucent occluders, or patching. Small-angle diplopia may respond to prism grind glasses. Botulinum toxin may not be effective for the fibrotic changes of TED, according to the experts.

Health Canada has approved teprotumumab for injection for use in adults for the treatment of moderate to severe active TED. Teprotumumab binds to IGF-1R, which plays a key role in regulating the pathological autoimmune activation of orbital fibroblasts in TED and blocks its activation and signalling. It is available as a 500 mg lyophilized powder for solution for IV infusion, and the dosage recommended in the product monograph is 10 mg/kg for the initial dose, followed by an IV infusion of 20 mg/kg every 3 weeks for 7 additional infusions.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 3 multicentre, double-masked, RCTs (TED01RV: a phase II study; TEP-301: a phase III study; and TEP-303: a phase III study) in patients with moderate to severe active TED; 3 long-term studies (off-treatment follow-up periods of the TED01RV trial and the TEP-301 trial, and an OLE of the TEP-301 trial); 2 ITCs, and 1 study addressing gaps in the evidence
- patients' perspectives gathered by 1 patient group, the Thyroid Foundation Canada (TFC)
- input from public drug plans that participate in the reimbursement review process
- 3 clinical specialists with expertise in diagnosing and treating patients with TED
- input from 1 clinician group, the Canadian Society of Oculoplastic Surgery (CSOPS)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to teprotumumab
- information submitted as a part of the sponsor’s request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

- One patient group, TFC, submitted input for this review. It is a nonprofit registered volunteer organization and charity, with a mission to awaken public interest in, and awareness of, thyroid disease; lend moral support to patients with thyroid disease and their families; and assist in fundraising for thyroid disease research. The information in this submission was gathered by TFC through 1 online survey and 3 telephone interviews with patients being treated with teprotumumab and living in the US. The data collected from the survey and telephone interviews were anonymized when aggregated for analysis. A total of 42 participants (37 patients and 5 caregivers) responded to the online survey. The majority of the patient respondents (almost 95%) were from Canada, with the remainder from the UK and the US.
- Patients with TED indicated that they experienced a range of symptoms, with light sensitivity, bulging eyes, dry and irritated eyes, and eye bags reported as always occurring by more than 40% of the respondents. Double vision and eyelid retraction were most often cited as always occurring by the caregivers. The respondents reported that dry and/or gritty eyes, light sensitivity, bulging eyes, and pressure or pain behind the eye were the most burdensome ocular symptoms. Patient respondents noted that TED negatively impacted their daily life and/or quality of life, with the most frequent issues being a negative impact on emotional and/or psychological well-being, social life, work or school life, ability to pursue hobbies, financial situation, family life, and ability to travel.
- Key outcomes noted as important by patients included improvement in signs and symptoms (less swelling, less eye pain, reduced redness, no sensitivity to light), reduced side effects, and reversal of disease.
- Three patients who were treated with teprotumumab shared their experience and noted positive responses with manageable side effects, although these responses were not instantaneous.

Clinician Input

- Clinical experts reported that active TED is associated with conjunctival injection, chemosis, caruncular injection, worsening proptosis, pain on eye movement, diplopia, and vision loss. The functional goal of treatment, as identified by the clinical experts, is a reduction in inflammation with preservation of vision, avoidance of diplopia, and comfort. According to the experts, a decrease in orbital inflammation is often reflected by a decrease in proptosis, although proptosis may remain in patients who become quiescent. The experts also reported that decreasing proptosis often decreases corneal exposure and improves patient appearance, which can affect patients psychologically.
- The clinical experts reported that limitations associated with current treatments include limited effectiveness, a lack of disease-modifying effects, and a risk of thyroid-associated orbitopathy recurrence despite treatment. The experts also noted that immunosuppressants cannot be used in patients with liver failure or tuberculosis, and glucocorticoid therapy can be associated with systemic AEs that can be both short- and long-term. Access to safer and more convenient

immunosuppressives — via oral, nasal, or subcutaneous routes, for example — would increase the convenience of delivery, according to the experts. High costs of therapies — especially teprotumumab and, to a lesser degree, tocilizumab — were highlighted by the experts.

- The experts stated that teprotumumab should not be considered as a first-line treatment. Rather, use of teprotumumab should be reserved for patients with moderate to severe active TED if there is an incomplete or no response to methylprednisolone and other currently available treatment options.
- All the engaged clinical experts reported that patients with new-onset disease and CAS equal or higher than 4 would respond best to treatment with an immunosuppressive; for example, teprotumumab, tocilizumab, or IVMP. The experts highlighted that patients with marked proptosis, vision loss, and progressive diplopia would also benefit from immunosuppression. Of note, the experts highlighted that teprotumumab should be used with increased caution in patients with existing hearing loss or in patients with diabetes, and it should not be used in patients who are pregnant or in patients who are still growing. The following considerations before initiating teprotumumab therapy were highlighted by the experts: whether the patient has an absolute contraindication to corticosteroids (e.g., previous psychosis), the differentiation of active versus chronic disease, and mitigation of risk factors (such as considerations for tobacco-use cessation).
- The clinical experts agreed that the outcomes of interest include vision, double vision (diplopia), corneal exposure, dry eye, and the ability to engage in social activities. One expert reported that a clinically meaningful response to treatment might correspond with a reduction in proptosis of more than 2 mm.
- Regarding the assessment of treatment response, the experts stated that a basic eye exam can be performed every 3 to 6 weeks before infusion, and a more detailed exam can be performed at 24 weeks and 48 weeks. Throughout treatment, patients should be monitored for systemic side effects by an endocrinologist or rheumatologist, according to the experts.
- The clinical experts agreed that teprotumumab should be discontinued if no evidence of a meaningful benefit is observed (i.e., no decrease in inflammation assessed through CAS, no decrease in proptosis, absence of reduction in double vision). All experts agreed that the drug should be suspended in the case of AEs, such as poorly controlled diabetes mellitus, hearing loss, or infection.
- The clinical experts agreed that ophthalmologists specializing in orbital pathology and TED or neuro-ophthalmologists would be required for diagnosis, to determine treatment eligibility, to initiate treatment, and to monitor and treat possible AEs. The experts also suggested that teprotumumab treatment should not be managed by otolaryngologists specializing in head and neck surgery, endocrinologists, or general ophthalmologists. According to the expert clinical panel, consideration should be given to screening audiometry before commencing therapy.
- The experts noted that an appropriate setting for treatment with teprotumumab will include an outpatient setting and, ideally, a multidisciplinary clinic with access to an oculoplastic surgeon or neuro-ophthalmologist, endocrinologist, and rheumatologist experienced with TED. Regarding restrictions to access in remote areas or smaller centres across the country, the experts reported that initial treatment decisions, initiation of therapy, and final evaluation post treatment would require

a specialist at the level of a tertiary care centre, but that the actual treatment over the 24 weeks of therapy could be administered and monitored through local IV clinics or local home care clinics.

Clinician Group Input

- CSOPS provided input for this submission. CSOPS represents a group of ophthalmic surgeons who have additional training and experience in the highly specialized fields of eyelid, orbit, nasolacrimal system, and facial aesthetics. A total of 29 clinicians provided their input.
- The clinician group indicated that an ideal treatment would avoid disease onset, delay progression, reduce signs and symptoms, preserve intact vision, and avoid negative impacts on quality of life.
- The clinician group noted that active TED will most likely respond to teprotumumab. Patients whose disease inadequately responds to steroids or who are unable to tolerate treatment with steroids, and patients with proptosis and/or diplopia, would be in most need of an alternative intervention. Regarding patients' responses to treatment, a clinically meaningful response would need to be assessed using trial outcome metrics — namely, proptosis reduction of 2 mm or more at week 24 of treatment. In the clinical setting, ophthalmologists would be assessing patients for a decrease in inflammation seen on a clinical exam, stability or an improvement of diplopia, proptosis, lid retraction, lid swelling, visual acuity, and redness.
- The clinician group highlighted that severe infusion reactions may necessitate discontinuation of treatment.
- The clinician group noted that the drug could also be prescribed by an endocrinologist, internal medicine physician, or immunologist; however, treatment should be followed by an ophthalmologist to assess treatment response.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for teprotumumab:

- relevant comparators
- consideration for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability
- system and economic issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies in Active TED

Three multicentre, double-masked, RCTs (i.e., TED01RV: a phase II study, N = 87; TEP-301: a phase III study, N = 83; and TEP-303: a phase III study, N = 54) assessed the efficacy and safety of teprotumumab relative to placebo in patients with moderate to severe active TED, with CAS values greater than or equal to 3 (TEP-303) or greater than or equal to 4 (TED01RV, TEP-301). The primary outcome of the TED01RV trial was overall responder rate (ORR), defined as the proportion of patients with at least a 2 mm reduction in proptosis and at least a 2-point reduction in CAS from baseline to 24 weeks in the study eye without corresponding deterioration in the fellow eye. In the TEP-301 and TEP-303 trials, the primary outcome was proptosis responder rate, defined as the proportion of patients with at least a 2 mm reduction from baseline to 24 weeks in proptosis in the study eye without corresponding deterioration in the fellow eye. The trials were conducted across 39 sites, with 24 centres in Europe, Japan, and the US, and no sites in Canada. Regarding baseline characteristics, across the studies, the mean age was approximately 50 and 51 years among patients from the teprotumumab and placebo groups, respectively. The proportion of female patients was approximately 67% (in the teprotumumab group) and approximately 76% (in the placebo group) across the trials. In the TED01RV and TEP-301 trials, more than 85% of patients were white. The TEP-303 trial was conducted in patients of Asian ethnicity. Regarding tobacco use, the proportion who currently use tobacco in the TEP-301 and TEP-303 trials was generally balanced between the study groups (22% teprotumumab versus 19% placebo in the TEP-301 trial; 14.8% teprotumumab versus 14.8% placebo in the TEP-303 trial), whereas in the TED01RV trial, more patients were currently using tobacco in the placebo group (40.9%) compared to the teprotumumab group (25.6%). Mean time since diagnosis of TED was approximately 5 months across the 2 treatment groups in the TED01RV and TEP-303 trials, and approximately 6 months across the 2 treatment groups in the TEP-301 trial.

Efficacy Results (Active TED Trials [TED01RV, TEP-301, TEP-303])

Overall Responder Rate

At week 24, the proportion of patients experiencing overall response across the teprotumumab and placebo arms, respectively, was 69.0% and 20.0% in the TED01RV trial, 78.0% and 7.1% in the TEP-301 trial, and 77.8% and 3.7% in the TEP-303 trial. In the TED01RV, TEP-301, and TEP-303 trials, the corresponding difference in ORR between teprotumumab and placebo group at 24 weeks was 50.32% (95% CI, 32.11% to 68.52%; $P < 0.0001$), 70.82% (95% CI, 55.89% to 85.75%; $P < 0.001$), and 74.07% (95% CI, 56.9% to 91.3%; $P < 0.0001$), respectively.

Proptosis Responder Rate

At week 24, the proportion of patients experiencing response in proptosis in the study eye across the teprotumumab and placebo arms, respectively, was 71.4% and 20.0% in the TED01RV trial, 82.9% and 9.5% in the TEP-301 trial, and 88.9% and 11.1% in the TEP-303 trial. The reported difference in proptosis responder rate between teprotumumab and placebo group at 24 weeks was 52.45% (95% CI, 34.39 to

70.51; P < 0.0001), 73.45% (95% CI, 58.89% to 88.01%; P < 0.001), and 77.78% (95% CI, 60.7% to 94.8%; P < 0.0001) for the TED01RV, TEP-301, and TEP-303 trials, respectively.

Diplopia Responder Rate

At week 24, the proportion of patients experiencing response in diplopia across the teprotumumab and placebo arms, respectively, was 68.4% and 25.6% in the TED01RV trial, 67.9% and 28.6% in the TEP-301 trial, and 63.6% and 45.0% in the TEP-303 trial. In the TED01RV trial, the integrated summary of efficacy analyses demonstrated a between-group difference in diplopia responder rate of 39.51% (95% CI, 17.78% to 61.24%; P = 0.0004). In the intention-to-treat (ITT) population of the TEP-301 trial, the difference in diplopia responder rate in the study eye between the teprotumumab and placebo groups at 24 weeks was 39.29% (95% CI, 15.55% to 63.02%; P = 0.001). In the ITT population of the TEP-303 trial, the difference in binocular diplopia responder rate between the teprotumumab and placebo groups at 24 weeks was 16.82% (95% CI, −11.4% to 45.1%; P = 0.2430).

Complete Diplopia Responder Rate at Week 24

Complete diplopia response was not analyzed in the TED01RV and TEP-301 trials. In the ITT population of the TEP-303 trial, the proportion of patients experiencing response in complete binocular diplopia at week 24 was 50.0% in the teprotumumab arm and 20.0% in the placebo arm. The difference in complete binocular diplopia responder rate between the teprotumumab and placebo group at 24 weeks was 29.09% (95% CI, 0.9% to 57.3%; P = 0.043).

Change From Baseline in GO-QoL Visual Function Score

At week 24, the mean (standard error) change from baseline in GO-QoL visual function score across the teprotumumab and placebo arms, respectively, was 21.10 (2.90) and 6.80 (2.66) in the TED01RV trial, 12.39 (2.98) and 4.21 (3.03) in the TEP-301 trial, and 16.22 (3.96) and 4.39 (3.97) in the TEP-303 trial. Trial findings of the assessment of change from baseline in GO-QoL visual function subscale demonstrated a difference of 14.30 (95% CI, 6.66 to 21.94; P < 0.001), 8.18 (95% CI, 0.59 to 15.76; P = 0.035), and 11.83 (95% CI, 1.82 to 21.83; P = 0.0215) for the comparison of teprotumumab to placebo in the TED01RV, TEP-301, TEP-303 trials, respectively.

Change From Baseline in GO-QoL Appearance Score

At week 24, the mean (standard error) change from baseline in GO-QoL appearance score across the teprotumumab and placebo arms, respectively, was 12.92 (2.84) and 6.60 (2.66) in the TED01RV trial, 14.43 (2.40) and 4.22 (2.41) in the TEP-301 trial, and 19.35 (3.93) and 8.69 (3.93) in the TEP-303 trial. Results assessing change from baseline in GO-QoL appearance subscale demonstrated a difference of 6.32 (95% CI, −1.25 to 13.90; P = 0.101), 10.21 (95% CI, 4.10 to 16.32; P = 0.001), and 10.66 (95% CI, 1.04 to 20.28; P = 0.0306) for the comparison of teprotumumab to placebo in the TED01RV, TEP-301, TEP-303 trials, respectively.

Harms Results (Active TED Trials [TED01RV, TEP-301, TEP-303])

In the active TED trials, most patients experienced more than 1 treatment-emergent AE (TEAE) during the treatment period (teprotumumab arms range: 74.4% to 92.6%; placebo arms range: 69.0% to 77.8%).

Serious TEAEs were more common across the teprotumumab arms (range: 3.7% to 11.6%) than in the placebo arms (range: 0% to 2.4%) across the studies. Discontinuation of treatment due to AEs was reported in 5 patients (11.6%), 1 patient (2.4%), and 1 patient (3.7%) in the teprotumumab arms of the TED01RV, TEP-301, and TEP-303 trials, respectively. One patient from the placebo groups of each study discontinued treatment due to an AE (TED01RV [2.3%], TEP-301 [2.4%], and TEP-303 [3.7%]). No deaths were reported in any of the trials conducted in patients with active TED. The rates of notable harms were higher in the teprotumumab arms (range: 18.6% to 48.8%) compared to the placebo arms (range: 2.3% to 23.8%). The range of specific notable harms reported across the trials were muscle spasm (teprotumumab: 11.1% to 31.7%; placebo: 0% to 9.5%), infusion-related reactions (teprotumumab: 3.7% to 14.6%; placebo: 0% to 9.5%), diarrhea (teprotumumab: 9.8% to 14.0%; placebo: 3.7% to 11.9%), and hyperglycemia (teprotumumab: 4.9% to 22.2%; placebo: 0% to 4.5%). Hearing impairment was reported in the TEP-301 and TEP-303 trials (teprotumumab: 9.8% to 14.8%; placebo: 0% to 3.7%).

Critical Appraisal (Active TED Trials [TED01RV, TEP-301, TEP-303])

Three randomized, double-masked, multicentre studies in patients with active TED were submitted by the sponsor for the current review. Treatment allocation was appropriately performed through a central interactive voice and web response system (in the TED01RV and TEP-301 trials) or electronic data capture (in the TEP-303 trial). However, there was a notable imbalance in key prognostic factors (e.g., uneven distribution of patients using tobacco in the TED01RV trial, and variability in patients' sex in the TED01RV and TEP-303 trials) between the teprotumumab and placebo arms, which could have impacted the observed intervention effects.

The risk of performance bias due to the knowledge of treatment assignment might have occurred in all the trials, despite the double-masked design, because patients in the teprotumumab groups experienced more notable harms (hyperglycemia, hearing impairment, muscle spasms, and so forth) compared to the placebo groups.

The clinical experts consulted noted 2 issues with the measurement of outcomes in the trials: potential inaccuracy and low reproducibility of Hertel measurements for proptosis (however, the masking of observers would have ensured that any measurement error was evenly distributed across the 2 arms, with observed differences not completely attributed to errors), and the subjective nature of the measurement of diplopia.

Multiplicity control using hierarchical testing procedures was adopted across the trials. However, the following outcomes were assessed only descriptively due to the failed hierarchy: GO-QoL appearance score (in the TED01RV trial), and diplopia responder rate, complete binocular responder rate, GO-QoL overall score, visual functioning, and appearance scores (in the TEP-303 trial). Subgroup analyses were conducted in the TEP-301 and TEP-303 trials (for tobacco use, age, and sex), but none of the subgroup comparisons were adjusted for multiplicity.

Overall, the clinical experts consulted for the review noted that the results from the 3 sponsor-submitted trials on active TED were generalizable to the context in Canada despite some potential issues. First, from the perspective of the real-world clinical practice, the eligibility criteria of the 3 trials may not be aligned with the anticipated target population for teprotumumab. The experts indicated that, ideally, the effects of

teprotumumab treatment should have been tested in patients with more severe disease, those with sight-threatening disease, or those with inadequate response to prior therapies. Second, preservation of vision is an important treatment goal identified by the patients, clinicians, and clinical groups consulted, but it was not assessed in the studies of teprotumumab. Instead, primary outcomes of active TED trials included measures of proptosis, which, even though they were identified as important by some patients and clinical groups and could influence quality of life, were considered of limited clinical relevance according to the panel of clinical experts consulted. Third, the duration of the trials (24 weeks) was not long enough to assess the effectiveness and long-term safety of teprotumumab. Lastly, most of the study populations in the TED01RV and TEP-301 trials were white, and the study population in the TEP-303 trial was of Asian ethnicity, which does not reflect the multicultural setting of Canada.

GRADE Summary of Findings and Certainty of the Evidence

Following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, the ranking of certainty in the evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (if a threshold was available) or to the null.

For the GRADE assessments, findings from active TED trials were considered together and summarized narratively per outcome and per comparison because these studies were similar in population, interventions, design, and outcome measures.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

Active TED:

- Proptosis responder rate
- ORR
- Diplopia responder rate and complete binocular diplopia responder rate
- HRQoL outcomes: GO-QoL questionnaire visual functioning and appearance subscales
- Harms: hyperglycemia and hearing impairment

Additional findings from the CAS measures in the active TED trials are provided as supportive evidence in the systematic review section of this report.

Table 1: Summary of Findings for Teprotumumab Versus Placebo for Patients With Active TED

Outcome and follow-up	Patients, N (studies)	Effect	Certainty	What happens
Proptosis				
Proptosis responder rate, % (95% CI) (≥ 2 mm reduction from baseline in proptosis in the study eye without deterioration [≥ 2 mm increase in the fellow eye]) Follow-up: Week 24	N = 224 (3 RCTs)	TED01RV trial[a]: • Teprotumumab: 71.4 (NR) • Placebo: 20.0 (NR) • Difference: 52.45 (34.39 to 70.51) TEP-301 trial: • Teprotumumab: 82.9 (NR) • Placebo: 9.5 (NR) • Difference: 73.45 (58.89 to 88.01) TEP-303 trial: • Teprotumumab: 88.9 (NR) • Placebo: 11.1 (NR) • Difference: 77.78 (60.7 to 94.8)	High[b,c,d]	Teprotumumab results in a higher proptosis responder rate when compared with placebo.
Overall responder rate				
Overall responder rate, % (95% CI) (≥ 2 mm reduction in proptosis **and** ≥ 2 point reduction in CAS from baseline in the study eye, provided there was no corresponding deterioration [≥ 2 mm/point increase] in proptosis or CAS in the fellow eye) Follow-up: at 24 weeks	N = 224 (3 RCTs)	TED01RV trial[a]: • Teprotumumab: 69.0 (NR) • Placebo: 20.0 (NR) • Difference: 50.32 (32.11 to 68.52) TEP-301 trial: • Teprotumumab: 78.0 (NR) • Placebo: 7.1 (NR) • Difference: 70.82 (55.89 to 85.75) TEP-303 trial: • Teprotumumab: 77.8 (NR) • Placebo: 3.7 (NR) • Difference: 74.07 (56.9 to 91.3)	High[b,e]	Teprotumumab results in a higher overall responder rate when compared with placebo.
Diplopia				
Diplopia responder rate, % (95% CI) (a ≥ 1-grade reduction among patients with diplopia > 0 at baseline) Follow-up: at week 24	N = 224 (3 RCTs)	TED01RV trial[a,f]: • Teprotumumab: 68.4 (NR) • Placebo: 25.6 (NR) • Difference: 39.51 (17.78 to 61.24) TEP-301 trial: • Teprotumumab: 67.9 (NR) • Placebo: 28.6 (NR) • Difference: 39.29 (15.55 to 63.02) TEP-303 trial[f]: • Teprotumumab: 63.6 (NR) • Placebo: 45.0 (NR) • Difference: 16.82 (−11.4 to 45.1)	Moderate[g,h,i]	Teprotumumab likely results in a higher diplopia responder rate when compared with placebo.

Outcome and follow-up	Patients, N (studies)	Effect	Certainty	What happens
Complete binocular diplopia responder rate, % (95% CI) (a diplopia score of 0 among patients with binocular diplopia > 0 at baseline) Follow-up: at week 24	N = 54 (1 RCT)	TED01RV trial: • Not assessed TEP-301 trial: • Not assessed TEP-303 trial[f]: • Teprotumumab: 50.0 (NR) • Placebo: 20.0 (NR) • Difference: 29.09 (0.9 to 57.3)	Low[j,h,k]	Teprotumumab may result in a higher complete binocular diplopia responder rate when compared with placebo.
HRQoL				
Change from baseline in the GO-QoL questionnaire visual functioning subscale, mean (95% CI) Follow-up: at week 24	N = 224 (3 RCTs)	TED01RV trial: • Teprotumumab: 21.10 (NR) • Placebo: 6.80 (NR) • Difference: 14.30 (6.66 to 21.94) TEP-301 trial[f]: • Teprotumumab: 12.39 (NR) • Placebo: 4.21 (NR) • Difference: 8.18 (0.59 to 15.76) TEP-303 trial[f]: • Teprotumumab: 16.22 (NR) • Placebo: 4.39 (NR) • Difference: 11.83 (1.82 to 21.83)	Moderate[l]	Teprotumumab likely results in an increase in GO-QoL visual functioning when compared with placebo.
Change from baseline in the GO-QoL appearance questionnaire subscale, mean (95% CI) Follow-up: at week 24	N = 224 (3 RCTs)	TED01RV trial[f]: • Teprotumumab: 12.92 (NR) • Placebo: 6.60 (NR) • Difference: 6.32 (−1.26 to 13.90) TEP-301 trial[f]: • Teprotumumab: 14.43 (NR) • Placebo: 4.22 (NR) • Difference: 10.21 (4.10 to 16.32) TEP-303 trial[f]: • Teprotumumab: 19.35 (NR) • Placebo: 8.69 (NR) • Difference: 10.66 (1.04 to 20.28)	Moderate[m]	Teprotumumab likely results in an increase in GO-QoL appearance when compared with placebo.
Harms				
Safety (hyperglycemia)	N = 224 (3 RCTs)	TED01RV trial: • Teprotumumab: 140 per 1,000 • Placebo: 45 per 1,000 TEP-301 trial: • Teprotumumab: 49 per 1,000 • Placebo: 0 per 1,000 TEP-303 trial:	Moderate[n]	Teprotumumab likely results in an increase in hyperglycemia when compared with placebo.

Outcome and follow-up	Patients, N (studies)	Effect	Certainty	What happens
		• Teprotumumab: 222 per 1,000 • Placebo: 37 per 1,000		
Safety (hearing impairment)	N = 224 (3 RCTs)	TED01RV trial: • Not assessed TEP-301 trial: • Teprotumumab: 98 per 1,000 • Placebo: 0 per 1,000 TEP-303 trial: • Teprotumumab: 148 per 1,000 • Placebo: 37 per 1,000	Moderate[n]	Teprotumumab likely results in an increase in hearing impairment when compared with placebo.

CAS = Clinical Activity score; CDA-AMC = Canada's Drug Agency; CI = confidence interval; GO-QoL = Graves ophthalmopathy quality-of-life questionnaire; HRQoL = health-related quality of life; MID = minimal important difference; NR = not reported; RCT = randomized controlled trial; TED = thyroid eye disease.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]The TED01RV trial analyzed responder rates using a logistic regression model. To increase consistency and enable comparison between different studies in active TED, the sponsor conducted additional efficacy analyses of TED01RV trial data using the Cochran-Mantel-Haenszel test (adjusted for tobacco use status).

[b]Did not rate down for concerns with study limitations. Imbalances in baseline characteristics of patients were observed for tobacco-use status and sex (TED01RV), and sex (TEP-303), suggesting a possible impact on the randomization. According to the clinical experts consulted, inaccuracy with Hertel measurements of proptosis is common, and reproducibility of measurement with this instrument is low. However, the CDA-AMC team deemed that the magnitude of differences in the response rates observed cannot be largely attributed to sampling or measurement error.

[c]Did not rate down for indirectness. Clinical experts consulted reported that teprotumumab treatment should have been tested in patients with more severe disease, those with sight-threatening disease, or those with inadequate response to prior therapies, which would be more aligned with the anticipated population of interest in the clinical setting in Canada. Even though some patient and clinical groups identified proptosis as an important outcome influencing quality of life, the clinical experts consulted considered proptosis to have limited clinical relevance.

[d]Did not rate down for imprecision. According to the clinical experts consulted by the review team, a between-group difference > 2 mm in proptosis is considered clinically important (i.e., MID). However, there are no established MIDs for between-group difference in proptosis responder rate; hence, the threshold of null was used.

[e]Did not rate down for indirectness. Clinical experts consulted reported that teprotumumab treatment should have been tested in patients with more severe disease, those with sight-threatening disease, or those with inadequate response to prior therapies, which would be more aligned with the anticipated population of interest in the clinical setting in Canada.

[f]Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[g]Rated down 1 level for serious concerns with study limitations. According to the clinical experts consulted, the subjective measurement of outcome adopted in the trial is inappropriate for assessing the effects of teprotumumab on diplopia. Moreover, imbalances in baseline characteristics of patients were observed for tobacco-use status and sex (TED01RV) and sex (TEP-303), suggesting a possible impact on the randomization.

[h]Did not rate down for indirectness. Clinical experts consulted reported that teprotumumab treatment should have been tested in patients with more severe disease, those with sight-threatening disease, or those with inadequate response to prior therapies, which would be more aligned with the anticipated population of interest in the clinical setting in Canada. Clinical experts consulted by CDA-AMC reported that complete binocular diplopia is an outcome of high importance among patients with TED.

[i]Did not rate down for imprecision. According to the clinical experts consulted by the review team, there are no established MIDs for between-group difference in diplopia responder rate; hence, the threshold of null was used. The lower bound of the 95% CI of the least squares mean change from baseline in diplopia responder rate in the TEP-303 trial included the null and the possibility of favouring placebo.

[j]Rated down 1 level for serious concerns with study limitations. According to the clinical experts consulted, the subjective measurement of outcome adopted in the trial is inappropriate for assessing the effects of teprotumumab on diplopia.

[k]Rated down 1 level for imprecision, given that the results were based on one study, with a limited sample size; the lower bound of 95% CIs was close to the value of null, indicating the possibility of no benefit.

[l]Imprecision was rated down for 1 level. According to the clinical experts consulted by the review team, a between-group difference of 6 points was considered clinically important (i.e., MID). The lower bound of the 95% CI of the change from baseline in the GO-QoL questionnaire visual functioning subscale was close to the MID (in the TED01RV trial) or crossed the MID (in the TEP-301 and TEP-303 trials).

[m]Imprecision was rated down for 1 level. According to the clinical experts consulted by the review team, a between-group difference of 6 points was considered clinically important (i.e., MID). The lower bound of the 95% CI of the change from baseline in the GO-QoL questionnaire appearance subscale included the possibility of favouring placebo (in the TED01RV trial) or the possibility of trivial benefit (in the TEP-301 and TEP-303 trials).

[n]Rated down 1 level for serious indirectness. The duration of follow-up of 24 weeks is inadequate for capturing the notable AEs of teprotumumab as per clinical expert panel input.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence, the TED01RV trial Clinical Study Report, the TEP-301 trial Clinical Study Report, and the TEP-303 trial Clinical Study Report.

Long-Term Extension Studies

Description of Studies

Two off-treatment follow-up periods (1 of the TED01RV trial and 1 of the TEP-301 trial) and 1 OLE of the TEP-301 trial (OPTIC-X) have been summarized in this section.

The TED01RV Trial: Follow-Up Period

This was an off-treatment follow-up period of 48 weeks (weeks 28 to 72) after the 24-week double-masked treatment period of the TED01RV trial. Patients were not allowed to be on additional treatment for TED during at least the first 12 weeks, unless medically indicated. The primary efficacy end point was ORR analyzed at week 28 and week 72 (defined as a decrease in overall CAS ≥ 2 points **and** a reduction in proptosis of 2 mm or more **and** no deterioration in the nonstudy eye [i.e., increase in CAS ≥ 2 points or increase in proptosis ≥ 2 mm]). A total of 76 patients (39 [86.7%] in the placebo group and 37 [88.1%] in the teprotumumab group) completed the study treatment (week 24). Of these, 74 patients (38 [84.4%] in the placebo group and 36 [85.7%] in the teprotumumab group) completed the off-treatment follow-up week 72 visit. Baseline characteristics were similar to those of the main trial as those patients entered the follow-up period.

The TEP-301 Trial: Follow-Up Period

The TEP-301 trial follow-up period was an off-treatment follow-up period of 48 weeks after the 24-week double-masked treatment period of the trial. Patients in the proptosis responder group, as well as those in the nonresponder group who chose not to enrol in the OPTIC-X trial, entered a follow-up period, during which the study drug was not administered. Patients who completed the 48-week treatment-free follow-up period had been off study drug for a total of 51 weeks at the time of the final visit (week 72). The primary efficacy end point was proptosis responder rate (defined as patients with a ≥ 2 mm reduction from baseline in proptosis in the study eye, without deterioration (≥ 2 mm increase) of proptosis in the fellow eye). A total of 79 patients (40 [95.2%] in the placebo group and 39 [95.1%] in the teprotumumab group) completed the study treatment period (week 24). Of these, 23 patients (3 [7.1%] in the placebo group and 20 [48.8%] in the teprotumumab group) completed the follow-up period (week 72). Relapse was defined as an increase in proptosis of 2 mm or more in the study eye since week 24 or an increase in CAS of 2 points or more since week 24 with an absolute CAS of 4 points or more following the week 24 visit. It was measured as the days from the week 24 visit date to the date that relapse criteria were met. In addition, patient symptomology was considered by the investigator to ensure relapse had occurred (e.g., new onset of double vision). Ten of the 41 patients (24.4%) who received teprotumumab relapsed and were discontinued from the follow-up period, and 9 of them enrolled in the OPTIC-X trial. Among the 4 patients in the placebo group who had data collected in the follow-up period, 1 met relapse criteria and was enrolled in the OPTIC-X trial.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

OPTIC-X was a phase III, multicentre, OLE trial of the safety and efficacy of teprotumumab in patients who completed the 24-week double-masked treatment period in the TEP-301 trial and whose proptosis did not respond to treatment or whose proptosis responded to treatment at week 24 but who met the criteria for re-treatment due to relapse during the follow-up period of the TEP-301 trial. Relapse was defined in a similar

manner as previously stated. The baseline (day 1) visit of this extension trial occurred within 14 days after the final visit of the TEP-301 trial (week 24 for those in the proptosis nonresponder group and up to week 72 for those whose proptosis responded to treatment but who relapsed). For patients whose proptosis did not respond to treatment or had received placebo in the TEP-301 trial and entered the OLE, they completed a 24-week treatment period, followed by a 24-week off-treatment follow-up period. For patients who entered the OPTIC-X study because they had responded to treatment and subsequently experienced relapse in the TEP-301 trial, there was no follow-up period after the OPTIC-X study treatment period. For these patients, the last clinic visit was at week 24 of the open-label treatment period.

Patients who had previously received placebo in the TEP-301 trial before entering the long-term OPTIC-X study were referred to as “first-course patients,” and those whose proptosis did not respond at week 24 of the TEP-301 trial or who experienced relapse during follow-up of the TEP-301 trial and enrolled into the OPTIC-X study were referred to as “second-course patients.” A total of 8 infusions of teprotumumab (10 mg/kg on day 1 followed by 20 mg/kg every 3 weeks for the remaining infusions) were administered during the 24-week treatment period. The primary efficacy end point was the proptosis responder rate (percentage of patients with a ≥ 2 mm reduction from baseline in proptosis in the study eye without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at week 24.

Of the 37 first-course patients (who received placebo in the TEP-301 trial), 36 (97.3%) were patients whose proptosis did not respond to treatment in the TEP-301 trial, and 1 (2.7%) experienced relapse during the TEP-301 trial follow-up period. Of the 14 second-course patients, 5 (35.7%) were patients whose proptosis did not respond in the TEP-301 trial, and 9 (64.3%) patients experienced relapse during the TEP-301 trial follow-up period. One patient in the second-course group did not complete the treatment period and did not continue in the follow-up period due to hospitalization (serious AEs of cerebral hemorrhage). Fifty-one patients (37 first-course and 14 second-course patients) were included in the OPTIC-X study. Most patients were female (first-course: 73.0%, second-course: 78.6%), white (first-course: 89.2%, second-course: 78.6%), and did not use tobacco (first-course: 78.4%, second-course: 78.6%). The mean time since diagnosis of TED was 12.26 months in the first-course group and 16.5 months in the second-course group.

Efficacy Results

Overall Responder Rate

The TED01RV Trial: Follow-Up Period

At week 72, the proportion of those in the overall responder group was 45.2% (19 of 42 patients) in the teprotumumab group compared to 22.2% (10 of 45 patients) in the placebo group, with a between-group difference of 23.0% (95% CI, 3.7% to 42.4%; P = 0.023).

The TEP-301 Trial: Follow-Up Period

The proportion of patients in the sustained overall responder group declined over time during the follow-up period relative to those in the responder group at week 24. Of the 32 patients in the teprotumumab group, 56.3% (18 of 32) were in the overall responder group at week 72. Of the 3 patients in the placebo group, 66.7% (2 of 3) were in the sustained overall responder group at week 72.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

Of the 24 patients in the first-course group who were in the overall responder group at week 24 relative to study baseline, 22 (91.6%) experienced a sustained response at week 48 of the OPTIC-X study. Of the 5 patients in the second-course group who were in the overall responder group at week 24 relative to study baseline (includes 1 patient whose proptosis did not respond in the TEP-301 trial and 4 who experienced relapse in the follow-up period of the TEP-301 trial), only 1 patient (initially in the proptosis nonresponder group in the TEP-301 trial) had experienced a sustained response at week 48 of the OPTIC-X study.

Proptosis (Responder Rate, Change From Baseline)

The TED01RV Trial: Follow-Up Period

The proportion of patients in the proptosis responder group was the same as the proportion in the overall responder group in both the teprotumumab and placebo groups at week 72. The mean change from baseline in the teprotumumab group was a reduction of 2.11 mm compared to a reduction of 1.13 mm in the placebo group at week 72.

The TEP-301 Trial: Follow-Up Period

Of the 34 patients whose proptosis had responded at week 24 of the double-masked treatment period, only 19 (55.9%) experienced a response at week 72 in the teprotumumab group, suggesting a decline in proptosis response over time. The mean change from baseline in proptosis was a reduction of 3.62 mm (mean percentage change from baseline: −16.27) (n = 21) in the teprotumumab group and a reduction of 2.67 mm (mean percentage change from baseline: −12.27) (n = 3) in the placebo group at week 72. Although the observed mean changes from baseline in proptosis were clinically meaningful at week 72, the sample sizes were small in both groups.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

The proportion of patients whose proptosis responded at week 24 relative to the study baseline was 89.2% (33 of 37) and 53.8% (7 of 13) in the first-course and second-course groups, respectively. Of those entering the OPTIC-X study from the TEP-301 study, 29 of the 32 patients (90.6%) in the first-course group and 1 of the 2 patients (50.0%) in the second-course experienced a sustained proptosis response at week 48 of the OPTIC-X study. Additionally, of the 1 patient in the first-course group and 9 patients in the second-course group whose disease relapsed during the follow-up period, all patients except 3 in the second-course group experienced a response at week 24 relative to the study baseline in the OPTIC-X study. Mean change from study baseline to week 24 in proptosis in the study eye was a reduction of 3.47 mm in first-course patients and a reduction of 1.77 mm in second-course patients. No additional results for change in proptosis were available during the follow-up period of the OPTIC-X study.

Diplopia Responder Rate

The TED01RV Trial: Follow-Up Period

Of the 36 patients in the teprotumumab group and 36 in the placebo group, 58.3% and 71.1% of patients, respectively, were considered to have experienced treatment response at week 72.

The TEP-301 Trial: Follow-Up Period

Of the 19 patients in the teprotumumab group who experienced diplopia response at week 24 in the double-masked treatment period, 57.9% (11 of 19) experienced sustained diplopia response at week 72. Of the 8 in the placebo group, 1 patient (12.5%) experienced a sustained diplopia response at week 72.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

The proportion of patients who experienced diplopia response at week 24 relative to the study baseline was 60.9% (14 of 23) and 75.0% (3 of 4) in first-course and second-course groups, respectively. Of the 14 first-course patients who were considered to have experienced diplopia response at week 24 relative to study baseline, 85.7% (12 of 14) experienced a sustained diplopia response at week 48 of the OPTIC-X study. Of the 3 second-course patients who experienced diplopia response at week 24 relative to study baseline, diplopia response was not sustained at week 48.

CAS (Responder Rate, Change From Baseline)

The TED01RV Trial: Follow-Up Period

At week 72, the mean change in CAS scores from baseline was a decrease of 3.8 points in the teprotumumab and placebo groups, indicating no difference between the groups at the end of the follow-up period.

The TEP-301 Trial: Follow-Up Period

Of the 24 patients who experienced a CAS response at week 24 of the double-masked treatment period, 50.0% experienced a sustained CAS response at week 72 in the teprotumumab group.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

The proportion who experienced CAS response at week 24 relative to the study baseline was 65.6% (21 of 32) and 36.4% (4 of 11) in the first-course and second-course groups, respectively. In the first-course group, of the 21 who experienced CAS response at week 24 relative to the study baseline (those who experienced proptosis nonresponse in the TEP-301 trial and CAS response in the OPTIC-X study at week 24), 20 (95.2%) patients had a sustained CAS response at week 48 of the OPTIC-X study. None of the patients in the second-course group had a sustained CAS response at week 48 of the OPTIC-X study.

Go-QoL Scores

The TED01RV Trial: Follow-Up Period

Only transformed scores for visual functioning and appearance subscales were available. Patients in both groups for both subscales observed an improvement in GO-QoL scores, with changes of greater than 10 compared to baseline values (except for the appearance scale scores at week 72 in the teprotumumab group).

The TEP-301 Trial: Follow-Up Period

When evaluated at week 72, for the 21 patients who received teprotumumab, a mean increase from baseline in GO-QoL overall transformed score was observed (21.19 points). For the subscales, a mean increase

from baseline in GO-QoL of 18.37 points for visual functioning (n = 33) and 27.98 points (n = 21) for the appearance scale was observed for patients in the teprotumumab group.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

There was a clinically meaningful improvement in overall GO-QoL scores for both groups. The mean increase from study baseline in GO-QoL–transformed overall score was similar in first-course and second-course patients in the OPTIC-X study (13.39 and 14.73, respectively). For the visual functioning subscale, the mean increase from study baseline was 11.73 and 23.21 in the first-course and second-course patients, respectively. For the appearance subscale, the mean increase from study baseline was 15.10 in the first-course patients and 6.25 in the second-course patients. These results suggest that an improvement in overall scores in the first-course and second-course patients was mainly driven by appearance and visual functioning, respectively.

Relapse

The TED01RV Trial: Follow-Up Period

Of the 30 patients who received teprotumumab, 11 (36.7%) patients who experienced proptosis response at week 24 did not maintain improvement relative to baseline (they experienced a reversal of ≥ 2 mm) during the off-treatment follow-up period at week 72.

The TEP-301 Trial: Follow-Up Period

Among the 33 patients treated with teprotumumab who experienced proptosis response at week 24 and entered the follow-up period, 10 (30.3%) patients experienced relapse during the follow-up period.

Harms Results

The TED01RV Trial: Follow-Up Period

The safety profile of teprotumumab did not change during the off-treatment follow-up period. No serious AEs or deaths were reported, and no AEs led to study discontinuation in the follow-up period.

The TEP-301 Trial: Follow-Up Period

Serious AE events were experienced in 2 (5.6%) patients in the teprotumumab group (intercostal neuralgia and optic neuropathy) during the follow-up period, which were considered severe in intensity and not related to the study drug. One patient in the teprotumumab group experienced a severe but not serious event of hypothyroidism (considered unrelated to teprotumumab) during the follow-up period. None of the AEs in the teprotumumab group led to discontinuation from the study. Three patients in the teprotumumab group had an AE of special interest during the follow-up period (diabetes mellitus, muscle spasms, and hypoacusis were experienced by 1 patient each).

Among the 4 patients in the placebo group in the follow-up period, 3 (75.0%) experienced at least 1 AE that was mild or moderate in intensity. None of the AEs in the placebo group was considered related to the study drug, was serious, or led to discontinuation from the study. None of the patients in the placebo group had an AE of special interest during the follow-up period.

No patient in either treatment group died during the follow-up period.

The TEP-302 Trial: TEP-301 OLE (OPTIC-X)

Of the 37 first-course patients, 32 (86.5%) reported 1 or more TEAEs, 26 (70.3%) reported 1 or more treatment-related TEAEs, 1 (2.7%) reported 1 or more TEAEs leading to withdrawal of the trial drug, and 1 (2.7%) patient reported 1 or more treatment-related TEAEs leading to permanent withdrawal of the trial drug. Similarly, in the 14 second-course patients, 11 (78.6%) patients reported TEAEs, 7 (50.0%) reported treatment-related TEAEs, 1 (7.1%) reported a serious TEAE (cerebral hemorrhage, considered not drug-related), and 1 (7.1%) reported a TEAE leading to permanent withdrawal of the trial drug.

The most common treatment-related TEAEs (≥ 10.0%) included diarrhea, muscle spasms, and dysgeusia in first-course patients and muscle spasms, nasal dryness, and dry skin in second-course patients. Among the 40 patients who entered the follow-up period, 7 (17.5%) patients had AEs considered treatment-related. Treatment-related AEs occurring in at least 2 patients (≥ 5.0%) during the follow-up period were muscle spasms (3 patients, 7.5%) and onycholysis (2 patients, 5.0%).

No deaths were reported in the treatment or follow-up period of the OLE.

TEAEs of special interest that occurred at any time during the treatment were hearing impairment (14.3% versus 10.8% in second-course patients and first-course patients, respectively), muscle spasms (28.6% versus 48.6%), diarrhea (7.1% versus 13.5%), and hyperglycemia (0% versus 8.1%). Two patients (1 first-course and 1 second-course) experienced AEs associated with hyperglycemia during the OPTIC-X study follow-up period. One patient (first-course) experienced neurosensory deafness during the follow-up period (considered not related to teprotumumab).

Critical Appraisal

In the 2 off-treatment follow-up periods of the TED01RV and TEP-301 trials, the proportion of responder rates (proptosis, diplopia, and overall) in the teprotumumab group decreased over time. Reduced sample sizes over time suggest a risk of attrition bias and raise concerns regarding the robustness of the follow-up efficacy outcome results. The impact of the use of concomitant medications on efficacy results during the follow-up period is unknown.

OPTIC-X was a phase III, multicentre, OLE of the TEP-301 trial with a 24-week treatment period and without a comparator group. A lack of a control group precludes causal statements about the benefit and harm. The open-label nature of the study may increase the risk of bias in determining the magnitude of the subjective outcomes, given that the lack of masking may impact patients' expectations of the treatment, particularly any subjective measures (such as quality of life). There was a decrease in response and sample sizes over time in the first-course patients, raising concerns regarding the long-term efficacy of the treatment. The data suggest that there was a lack of sustained response in second-course patients, making it challenging to evaluate whether those whose disease did not show response may benefit from an additional course of teprotumumab in the long term, so these results require additional confirmation. There was a risk of attrition bias, given that the number of patients contributing to the analyses declined steadily over time and final measures of the outcome at week 48 were based on a limited sample size. Because there was no

follow-up data for patients who had relapsed in the TEP-301 trial and were re-treated in the OPTIC-X study, no conclusions can be drawn regarding the sustained responses for those patients. Many patients used concomitant medications during the treatment period (i.e., sulphur-containing imidazole derivatives, thyroid hormones, glucocorticoids), and the effect of these on efficacy outcomes cannot be determined.

None of the trial sites were in Canada, reducing the generalizability and applicability of the results to clinical practice in Canada.

Indirect Comparisons

Description of Studies

The sponsor submitted 2 unanchored MAIC analyses comparing the effects of teprotumumab with IVMP in active TED. The first ITC (ITC 1) leveraged individual patient data from 2 teprotumumab trials (TED01RV and TEP-301) that were matched to the IVMP group of the 8 published studies, pooled via random-effects meta-analysis. Comparative treatment effects on outcomes of interest were reported, including mean difference in the change from baseline for proptosis and odds of diplopia response (reduction in diplopia of ≥ 1 grade). The base-case scenario incorporated 4 variables in the MAIC analyses (tobacco use, baseline diplopia, baseline proptosis, and radioiodine therapy). Matching to the IVMP trials for the MAIC analyses reduced the initial sample size of the teprotumumab trials (N = 84) to an effective sample size (ESS) of [redacted] (for proptosis MAIC) and [redacted] (for diplopia MAIC). The second ITC (ITC 2) used individual patient data from the same 2 teprotumumab trials (TED01RV and TEP-301), matched to IVMP group data from 5 published studies, to compare the effects of teprotumumab versus IVMP on quality of life using a random-effects meta-analysis. Change in GO-QoL (overall and subscale) from baseline to week 24 in patients receiving teprotumumab versus change in GO-QoL from baseline to week 12 in patients receiving IVMP were compared indirectly using unanchored MAIC analysis. The covariates included in the adjustment were severe diplopia, proptosis, tobacco-use status, baseline GO-QoL scores, female sex, and age. As CAS was deemed to be prognostically important for predicting GO-QoL changes, a sensitivity analysis was conducted. Post matching adjustment to IVMP studies, the ESS was 48 for total GO-QoL, 47 for appearance GO-QoL, and 49 for visual functioning GO-QoL for the base-case analysis. Post matching adjustment to IVMP studies, the ESS was 36 for total GO-QoL, 36 for appearance GO-QoL, and 36 for visual functioning GO-QoL for the sensitivity analysis.

Efficacy Results

For ITC 1, the base case adjusted MAIC analyses demonstrated a mean difference favouring teprotumumab for the proptosis outcome, with a reported change from baseline in proptosis of [redacted] (95% CI, [redacted]). For diplopia response, an adjusted odds ratio favouring teprotumumab was observed, with a reported value of [redacted] (95% CI, [redacted]) for teprotumumab versus IVMP comparison.

For ITC 2, the results of the MAIC for the primary analysis (moderate IVMP dose only) showed a mean difference in change from baseline of 13.26 (95% CI, 7.44 to 19.09) for overall GO-QoL scores, favouring teprotumumab versus IVMP. Results for the GO-QoL appearance subscale (mean difference in change from

baseline: 7.50, 95% CI, 0.35 to 14.64) and visual functioning subscale (mean difference in change from baseline: 17.66, 95% CI, 7.86 to 27.47) also favoured teprotumumab versus IVMP.

Harms Results

Sponsor-conducted ITCs did not evaluate the comparative safety of teprotumumab.

Critical Appraisal

ITC 1

In the absence of a common comparator, an unanchored MAIC was conducted by the sponsor. Inherent limitations with an unanchored MAIC include the inability to preserve randomization within each study and the chance of bias in the comparative efficacy estimate due to possible imbalances in prognostic factors across the trial populations. Furthermore, the sample size available for analyses was reduced due to the matching across groups. Although key baseline covariates were well balanced across the teprotumumab and IVMP cohorts following adjustment, the adjustment considered only 4 out of 11 variables that were preidentified by the sponsor as relevant. According to the experts consulted by CDA-AMC, important prognostic factors, such as diabetes, disease duration, and vision, were not included for the adjustment in the MAIC analyses. Thus, concerns remain that not all prognostic and effect-modifying factors were accounted for in the unanchored comparisons. Input from the clinical expert suggested that certain important treatments of interest for clinical practice in Canada (e.g., tocilizumab) were not considered in the ITC analyses. Considering all the aforementioned factors, it is likely that the MAIC estimates are subject to an unknown amount and direction of bias, leading to challenges to interpretation and uncertainty in the MAIC findings.

ITC 2

The sponsor-funded ITC followed standard systematic review methods; however, limitations included a lack of risk of bias assessments, unmasked IVMP studies, and no sensitivity analyses to explore potential biases. Considerable methodological heterogeneity was observed across IVMP studies — such as differences in dosing, disease duration, baseline characteristics, and study designs — which introduced uncertainty in the pooled effect estimates, particularly for the visual functioning subscale. Due to the limited availability of data and restrictions on the sample sizes available, not all relevant prognostic variables could be included (such as the presence of gaze-evoked orbital pain). Additionally, there was no consideration of effect modifiers or investigation of the potential extent of residual confounding, which may be substantial. Residual confounding remains likely, and the reduced ESS further decreases the reliability of results. A lack of protocol or statistical analysis plan increased the potential for selective outcome reporting. As a result, the ITC findings are highly uncertain. In addition, the comparisons were limited to teprotumumab and IVMP, with no information on comparative effects with other relevant comparators for clinical practice in Canada (i.e., tocilizumab, rituximab).

Studies Addressing Gaps in the Evidence From the Systematic Review

One published real-world study that evaluated the safety of teprotumumab compared to currently available off-label treatments in patients with TED was submitted by the sponsor.

Population

The study included patients aged 18 years and older with TED with a treatment code for teprotumumab or glucocorticoids between January 1, 2020, and December 1, 2024, from 80 health care organizations in the US (the TriNetX database). Patients with TED were defined as those with a diagnostic code for thyroid diseases (teprotumumab), or at least 1 diagnostic code for hyperthyroidism and at least 1 diagnostic code for eye symptoms related to TED (glucocorticoid groups) using International Classification of Diseases, 10th Revision (ICD-10) codes. Patients with a treatment code for teprotumumab and IV or oral glucocorticoids following a TED diagnostic code were included in the teprotumumab arm, IV glucocorticoid arm, and oral glucocorticoid arm, respectively. Patients who were pregnant were excluded from all groups.

Results

Baseline Characteristics

Before propensity score matching, 923 patients with TED who received teprotumumab, 3,613 who received IV glucocorticoids, and 4,243 who received oral glucocorticoids were included. After propensity score matching, 685 patients who received teprotumumab (mean age, 57.8 [SD = 13.9] years; 72.4% female), 685 who received propensity score–matched IV glucocorticoids (57.4 [SD = 14.7] years; 73.9% female), 741 who received teprotumumab (57.0 [SD = 14.2] years; 73.5% female), and 741 who received propensity score–matched oral glucocorticoids (57.0 [SD = 15.2] years; 73.5% female) were included. The baseline characteristics of patients in each group before propensity score matching were not described. Most baseline characteristics, including demographics, comorbidities, previous medications, socioeconomic status, health care utilization (including screening services), and laboratory data, were well balanced (SMD < 0.1). Some body measurements and laboratory data (i.e., body mass index, hemoglobin A1C, triiodothyronine) had a high frequency of missing data, and there is no evidence of how this was handled. Approximately 6% of patients with TED in the cohort had blindness or low vision, and approximately 48% of patients with TED had exophthalmic conditions. Around 40% of patients with TED in the cohort had been prescribed methimazole, and approximately 1.5% of patients with TED had been prescribed rituximab.

Harms

Compared to IV or oral glucocorticoids, treatment with teprotumumab was associated with a lower hazard of all-cause mortality (teprotumumab versus IV glucocorticoids: HR = 0.32; 95% CI, 0.16 to 0.65; teprotumumab versus oral glucocorticoids: HR = 0.20; 95% CI, 0.10 to 0.39).

Cardiovascular Outcomes

Patients in the teprotumumab group had a lower hazard of acute myocardial infarction compared to patients in the IV or oral glucocorticoids group (teprotumumab versus IV glucocorticoids: HR = 0.37; 95% CI, 0.15 to 0.95; teprotumumab versus oral glucocorticoids: HR = 0.33; 95% CI, 0.12 to 0.91). Compared to IV glucocorticoids, point estimates favoured teprotumumab for cerebral infarction, peripheral vascular diseases, heart failure, and atrial fibrillation, although all 95% CIs were wide and crossed 1. Compared to oral glucocorticoids, teprotumumab was associated with a lower hazard of cerebral infarction (HR 0.33, 95% CI 0.15 to 0.72), peripheral vascular disease (HR = 0.44; 95% CI, 0.21 to 0.91), heart failure (HR = 0.47; 95% CI 0.26 to 0.85), and atrial fibrillation (HR = 0.46; 95% CI 0.23 to 0.90).

Renal Outcomes

There was a lower hazard of acute kidney failure among patients who were exposed to teprotumumab compared to glucocorticoids (teprotumumab versus IV glucocorticoids: HR = 0.54; 95% CI, 0.31 to 0.94; teprotumumab versus oral glucocorticoids: HR = 0.37; 95% CI, 0.22 to 0.63). The point estimate for chronic kidney disease favoured teprotumumab compared to IV or oral glucocorticoids; however, the CIs were wide and crossed 1.

Other Safety Outcomes

There was a higher hazard of hearing loss among patients who initiated teprotumumab compared to glucocorticoids (teprotumumab versus IV glucocorticoids: HR = 2.43; 95% CI, 1.67 to 3.55; teprotumumab versus oral glucocorticoids: HR = 2.38; 95% CI, 1.65 to 3.44). There was no significant difference in the hazard of diabetes, inflammatory bowel disease, and need for a hearing device.

Infectious Outcomes

Among patients treated with teprotumumab versus IV or oral glucocorticoids, there was a lower hazard of urinary tract infections (teprotumumab versus IV glucocorticoids: HR = 0.60; 95% CI, 0.406 to 0.887; teprotumumab versus oral glucocorticoids: HR = 0.58; 95% CI, 0.396 to 0.859), pneumonia (teprotumumab versus IV glucocorticoids: HR = 0.368; 95% CI, 0.223 to 0.605; teprotumumab versus oral glucocorticoids: HR = 0.330, 95% CI, 0.204 to 0.533), and severe sepsis (teprotumumab versus IV glucocorticoids: HR = 0.240; 95% CI, 0.091 to 0.635; teprotumumab versus oral glucocorticoids: HR = 0.309; 95% CI, 0.114 to 0.836).

Critical Appraisal

The real-world evidence study by Lo et al. (2025) had several important methodological and reporting limitations, including the absence of a predefined protocol, limited information on confounder selection, low data quality and missing data handling, and no reporting of absolute effect estimates with CIs. Although an active-comparator new-user design was stated, key features such as lookback and washout periods were not described, introducing risks of prevalent user bias. Differences in selection procedures across groups also introduced a risk of selection bias and immortal time bias (particular to outcomes such as mortality). Propensity score matching reduced some imbalances, but residual confounding is likely, given issues with substantial missing data for some variables and a lack of clarity about whether the exclusion of participants with prior outcomes occurred before or after matching. Additional concerns included potential for outcome misclassification, differing follow-up durations between groups, small event numbers, unverified model assumptions, and lack of a prespecified analysis plan, raising the possibility of selective reporting. While the study benefits from a large US real-world sample, the generalizability of study findings to patients with TED in Canada is unknown, key harms such as hyperglycemia were not assessed, and the heterogeneous TED population limits applicability to patients with moderate to severe active TED.

Ethical Considerations

Patient group, clinician group, and drug plan input, as well as consultation with clinical experts, were reviewed to identify ethical considerations specific to the use of teprotumumab in adults for the treatment of moderate to severe TED.

Diagnosis, Treatment, and Experiences of People Living With TED

- Active TED can significantly affect patients' quality of life, particularly when inflammation and tissue expansion around the eyes lead to proptosis, eyelid retraction, and diplopia. Patient group input indicates that symptoms such as blurred or double vision and sensitivity to light can disrupt daily activities like reading, driving, and working. Even when TED does not threaten vision directly, constant eye pain and tearing can curtail independence, causing patients to withdraw from social or professional settings. Further, changes in physical appearance (e.g., proptosis and eyelid retraction) may contribute to stigma and psychological distress, with many patients reporting anxiety and depression related to the visible nature of their condition. These challenges extend to caregivers, who may shoulder emotional and logistical burdens. For example, they may need to assist with daily tasks and medical appointments and provide emotional support — often while navigating their own feelings and responsibilities.
- Clinical experts and patient group input indicate that TED diagnosis can be delayed if eye symptoms are subtle or if patients do not have timely access to specialists. Because vision care is not publicly funded across Canada (with some exceptions), individuals without private insurance may face additional barriers to accessing the ophthalmologic care necessary for diagnosis. These delays can postpone access to existing treatment options, increasing the risk of disease progression and exacerbating the physical and psychosocial burdens of living with TED.
- There are currently no disease-modifying treatment options for active TED, leaving patients to rely on therapies that primarily address symptoms or manage complications. Treatment for active TED involves the use of off-label therapies such as IVMP, a high-dose glucocorticoid, and immunomodulators like tocilizumab. Radiotherapy may also be used as an adjunct, but it can carry significant risks, including retinopathy, cataracts, and systemic side effects. Although these options are widely used to manage active inflammation, their accessibility varies across patient populations due to differences in insurance coverage and the geographic availability of clinical expertise. Clinical experts highlighted that surgery, particularly orbital decompression, is reserved for sight-threatening complications during the active phase. However, lack of access to surgical expertise and prolonged waiting times can present barriers for patients needing surgical intervention. Experts also noted that lifestyle modifications, such as tobacco-use cessation, could provide added benefit but may be challenging for some patients to sustain.
- Patient group input emphasized the need for treatments that go beyond symptom management to address the underlying cause of TED. It indicated that patients value interventions that minimize side effects, particularly those associated with steroid use (e.g., weight gain). Desired outcomes for new therapies include improvements in swelling, eye pain, redness, and light sensitivity, as well as the

potential for disease reversal. These priorities reflect a strong preference for therapies that not only alleviate symptoms but also enhance overall quality of life.

Clinical Evidence Used in the Evaluation of Teprotumumab

- The safety and efficacy of teprotumumab in adult patients aged 18 to 80 years with active TED were evaluated across 3 pivotal trials: TED01RV, TEP-301, and TEP-303. TED01RV was a phase II, randomized, placebo-controlled, double-masked trial (N = 87). The primary objective was to assess the ORR, defined as a 2 mm or more reduction in proptosis and a 2 point or more reduction in CAS, which assesses eye inflammation, from baseline at week 24. TEP-301 (N = 83) and TEP-303 (N = 54) were phase III, randomized, placebo-controlled, double-masked trials. They shared the same primary objective of assessing the proptosis responder rate, defined as a 2 mm or more reduction in proptosis from baseline in the study eye (without deterioration in the fellow eye) at week 24. Across all trials, patients in the active arm received an initial dose of 10 mg/kg of teprotumumab intravenously, followed by 20 mg/kg intravenously every 3 weeks until reaching a total of 8 doses. Results across all 3 studies suggest that treatment with teprotumumab results in higher proptosis and overall treatment response rates compared to placebo. Further details of these trials are provided in the clinical review report.
- The long-term efficacy and safety of teprotumumab in active TED are currently uncertain. The sponsor submitted long-term follow-up studies for the TED01RV and TEP-301 trials that extended the observation period by an additional 48 weeks each. The clinical review report notes that although results suggest there was a clinically meaningful proptosis reduction at the follow-up, challenges with trial dropouts and similar response rates across placebo and active arms limit confidence in these findings. Further, notable relapse rates for proptosis response were observed in both, ranging from 30.3% to 36.7%. Clinical experts expressed concern about the high cost of teprotumumab, given the uncertainty of long-term benefit. They were particularly concerned with relapse rates and diminishing differences between treatment and placebo groups. These findings underscore the challenges to assessing the long-term value of teprotumumab for the health care system.
- The OPTIC-X OLE study evaluated teprotumumab in TEP-301 participants who were either participants in the nonresponder or responder arm or in the placebo arm. Although some patients experienced an initial response during treatment, these effects were inconsistent over time, with diminishing proptosis, diplopia, and CAS responses by week 48. Clinical experts highlighted that this raises ethical concerns about whether re-treatment provides a sufficient long-term value, especially given the high cost of teprotumumab.
- Clinical experts indicated that the focus on reducing proptosis across all 4 trials may not fully capture the functional impact of TED on vision and people's ability to participate in daily activities. Although clinical experts acknowledged that patients often face significant psychosocial challenges due to proptosis and that reductions in proptosis may have an impact on quality of life, they considered the focus on proptosis reduction to have limited clinical relevance. Further, though some secondary and exploratory outcomes did assess teprotumumab's impact on diplopia, clinical experts suggested the subjective tools used to measure diplopia were inadequate and not consistent with clinical practice.

- Clinical experts indicated that eligibility criteria across all 4 trials limited the generalizability of trial results. The exclusion of people with optic neuropathy, a sight-threatening manifestation of TED, limits the applicability of findings for people at the greatest risk of vision loss. Additionally, excluding patients with recent steroid use creates uncertainty about how teprotumumab might perform in the typical clinical pathway in Canada. While these exclusions may be justified from a trial design perspective, they raise ethical considerations regarding the adequacy of evidence to guide real-world decision-making. Experts emphasized the need for long-term, real-world evidence to fill these gaps and support clinical decision-making in the future.

Clinical Use of Teprotumumab

- Clinical experts indicated that they would consider prescribing teprotumumab for the treatment of active TED. However, they also emphasized that it should not replace glucocorticoids as first-line therapy in Canada. Although teprotumumab has demonstrated the ability to reduce proptosis in a trial setting, experts were concerned that the lack of evidence for functional improvements to vision suggests this impact may have limited clinical relevance.
- Despite the clinical experts' view that teprotumumab may only have a “cosmetic” impact on active TED, patient input emphasized the importance of reducing proptosis and eye pain. This is especially significant given the visible nature of the condition and its effects on self-confidence and mental health. Even a cosmetic reduction in proptosis could be meaningful for some patients, offering psychosocial benefits by alleviating feelings of stigma and enhancing quality of life.
- Clinical experts raised concerns about emerging evidence on long-term hearing impairment associated with teprotumumab. They suggested that ototoxicity may have been underreported in trials due to the use of standard rather than high-frequency audiometric testing. They added that emerging real-world evidence from the US indicates potential long-term risks of hearing impairment (e.g., tinnitus and hearing loss) and reiterated the importance of further investigation into this risk. To mitigate the risks of ototoxicity, experts recommended more routine, higher frequency audiometric testing before initiating teprotumumab, given that patients with pre-existing hearing complications may be at a greater risk of experiencing impacts on their hearing. Further, they emphasized the need for robust postapproval studies and transparent communication with patients to support informed decision-making. In the absence of robust clinical evidence demonstrating a clear impact on visual function, clinical experts suspect that the willingness to accept these risks to hearing may be low.
- Clinical experts emphasized the importance of reserving teprotumumab for patients most likely to experience benefit, particularly those with moderate to severe active TED treated early. Diagnosis, treatment initiation, and monitoring for AEs will require oversight by specialists, such as ophthalmologists specializing in orbital pathology or neuro-ophthalmologists. Experts also acknowledged that these requirements could create access barriers for patients in rural or underserved areas. To address this, they suggested enabling follow-up care and infusions at local centres. This could be supported by virtual care to reduce travel burdens while maintaining specialist oversight for prescriptions and long-term monitoring.

Health Systems

- Based on the totality of the clinical evidence, teprotumumab is a high-cost immunosuppressant that reduces proptosis by 2 mm or more in eligible patients with active TED. However, clinical experts questioned whether this reduction justifies teprotumumab's significant cost to the health system, given their perception that the reduction in proptosis has limited clinical relevance. This raises broader concerns about sustainable resource allocation. This may be especially true when less expensive alternatives, such as off-label tocilizumab, have shown some benefit in real-world settings. Clinical experts emphasized the need for more robust comparative evidence to assess teprotumumab's comparative efficacy and cost-effectiveness relative to existing therapies. Such evidence is critical to supporting equitable clinical decision-making and ensuring health system sustainability.
- Clinical experts raised significant concerns about the uncertain long-term effectiveness and safety of teprotumumab in managing active TED. Questions remain about whether its effects on proptosis and inflammation are sustained over time, complicating assessments of cost-effectiveness and value to the health system. The pharmacoeconomic review concluded that teprotumumab is not cost-effective under current conditions. This raises further concerns about its financial sustainability, particularly if re-treatment is required.
- Additionally, hearing-related risks associated with teprotumumab remain a significant challenge, given that long-term safety data are lacking. Clinical experts noted that reports of hearing loss or impairments in patients from the US highlight the need for ongoing monitoring and real-world evidence to better understand the extent and durability of this adverse effect. Experts emphasized the importance of transparent reporting and careful postmarket surveillance to guide future reimbursement and clinical decisions.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with moderate to severe active TED
Treatment	Teprotumumab
Dose regimen	10 mg/kg for the initial dose followed by 20 mg/kg every 3 weeks, for 7 additional infusions
Submitted price	Teprotumumab: $9,776.41 per 500 mg single-dose vial
Submitted treatment cost	$215,175 per patient per treatment course, based on a patient weight of 73.37 kg[a]
Comparators	IVMP

Component	Description
Perspective	Publicly funded health care payer in Canada Societal perspective
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data sources	TED01RV and TEP-301 clinical trials for teprotumumab; unanchored MAICs to inform comparative efficacy vs. IVMP
Key limitations	• The submitted model structure (i.e., health states) is based on a composite outcome of diplopia and proptosis, as defined and separately measured in the clinical trials, which do not align with how these outcomes are used in treatment decisions. As such, the model does not reflect the clinical management of TED, lacking validity and reliability. Reduction in proptosis is considered of limited clinical relevance according to clinical expert feedback obtained by CDA-AMC, and the measurement of diplopia used in the trials is subjective and inappropriate to accurately capture treatment effects. Objective measures to assess diplopia (i.e., prism measurement) should have been adopted instead because they are more reflective of clinical management in practice. • Limitations identified with the clinical evidence (e.g., results for diplopia are uncertain; there was incomplete adjustment of important effect modifiers in the MAIC and restricted generalizability) resulted in considerable uncertainty in the estimates of cost-effectiveness of teprotumumab. The transition probabilities used in the model were based on a post hoc analysis using transformed results that could not be validated by CDA-AMC; as such, the reliability of the approach could not be validated. Further, as the transitions are based on the composite of diplopia and proptosis, they are subject to the aforementioned limitations with the outcome measures and largely driven by proptosis results. • The approach to modelling the long-term effectiveness of teprotumumab lacks face validity as it assumes no treatment waning, re-treatment, or relapse, which results in the majority of patients remaining indefinitely in healthier states after the initial 24 weeks, despite high rates of relapse and re-treatment with teprotumumab reported in follow-up or extensions of the pivotal trials and RWE. • Costs and disutilities due to teprotumumab-induced hearing loss were not included in the model. Postmarket evaluations raise concerns that the frequency and permanence of ototoxicity in clinical practice may be higher than reported in trials and associated with a lack of appropriate testing along with treatment (i.e., beyond standard audiometry). • The quality-of-life impact of teprotumumab is highly uncertain. Clinical expert feedback obtained by CDA-AMC raised concerns about the face validity of the assumptions and published utility values used by the sponsor. Health state utilities seemed underestimated compared to other published studies on blindness and postsurgery outcomes. The study selected by the sponsor is highly subject to conflicts of interest (e.g., the publication and various authors were funded by the sponsor). • Drug wastage costs were inappropriately excluded from the model because drug plan feedback indicated that vial sharing in an outpatient setting is unlikely for both teprotumumab and IVMP, given that they are expected to be reimbursed as single-use vials. • Other alternative treatments used in clinical practice were excluded from the model, most notably tocilizumab, which is used in place of teprotumumab in current clinical practice (accessible in some jurisdictions). The cost-effectiveness of teprotumumab vs. unmodelled comparators is therefore unknown. Clinical expert feedback noted that tocilizumab is expected to have a lower cost and fewer side effects. • The sponsor considered productivity costs when conducting the analysis from the societal perspective. However, costs and assumptions regarding patient and caregiver productivity were solely based on assumptions, lack face validity (e.g., no consideration of retirement,

Component	Description
	no consideration of reduced hours of employment vs. no employment, no productivity loss associated with teprotumumab treatment administrations) and bias the results in favour of teprotumumab. As such, the components included for the societal perspective could not be validated and are associated with uncertainty.
CDA-AMC reanalysis results	• No reanalyses were performed owing to limitations in the model structure and uncertainty in the clinical evidence that could not be resolved through reanalysis. • The societal perspective is not considered relevant due to concerns with the validity of the inputs and assumptions. • Based on the sponsor's results, from a health care payer perspective, teprotumumab is not cost-effective in active TED with an ICER exceeding $180,000 per QALY gained. If considering a WTP threshold of $50,000 per QALY gained, a 72% price reduction would be required to achieve cost-effectiveness of teprotumumab vs. IVMP for treatment of active TED. • CDA-AMC conducted a series of scenario analyses from the health care payer perspective. Based on the CDA-AMC multivariate scenario analysis that included 1 course of re-treatment, higher utility values after surgery, and wastage, the ICER for teprotumumab increased to $397,788 per QALY gained compared to IVMP.

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; IVMP = IV methylprednisolone; LY = life-year; MAIC = matching-adjusted indirect comparison; QALY = quality-adjusted life-year; RWE = real-world evidence; TED = thyroid eye disease; WTP = willingness-to-pay; vs. = versus.

Note: Teprotumumab is being reviewed by CDA-AMC through the complex review pathway; as such, CDA-AMC has appraised 2 cost-effectiveness analyses submitted by the sponsor, 1 adopting a publicly funded health care payer perspective and 1 adopting a societal perspective.

[a]The sponsor's estimated drug cost assumes that there is no drug wastage and that patients are treated for 24 weeks as per the product monograph.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: costs of re-treatment with teprotumumab were not included despite evidence suggesting high re-treatment rates; the uptake of teprotumumab is uncertain and may be lower than anticipated by the sponsor in moderate to severe active TED, specifically in first-line treatment; and the number of patients eligible for treatment is uncertain and may be higher than anticipated by the sponsor.

CDA-AMC did not conduct a base-case reanalysis due to a lack of clinical data and model flexibility to address concerns with re-treatment. In the sponsor's base case, the 3-year budget impact of reimbursing teprotumumab for the treatment of moderate to severe active TED in adult patients is expected to be $91,541,779 (year 1: $24,571,068; year 2: $29,849,450; and year 3: $37,121,261). The estimated budget impact is highly sensitive to re-treatment, uptake, and the number of patients eligible for treatment. When considering 1 course of re-treatment of 34% of patients who received teprotumumab in the first line, this corresponded to an additional budget impact of $20,237,169 (a 22% increase from the sponsor's estimates). Re-treatment after second-line or multiple courses of re-treatment would result in further increased costs to the health care system. A scenario analysis exploring the exclusion of teprotumumab from first-line use in active TED resulted in an estimated 3-year budget impact of approximately $59 million (35% lower than the sponsor estimates).

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for teprotumumab for adult patients with moderate to severe active TED. In their request, the sponsor identified the following issues:

- CDEC's discussion points did not consider the rarity and severity of moderate to severe active TED. The sponsor stated that moderate to severe active TED is a rare and serious disease and requested that the submitted evidence be appraised within this context, an important consideration within the unmet clinical need domain of the CDA-AMC deliberative framework.
- The sponsor is of the view that teprotumumab is the only disease-modifying therapy in TED and that existing off-label treatments do not modify the core pathophysiology of moderate to severe active TED.
- CDEC concluded that the ITC had insufficient evidence to determine the comparative clinical effect of teprotumumab versus current treatments in Canada. The sponsor is of the view that although the submitted ITC and RCTs have points of uncertainty, the evidence is not insufficient.
- CDEC's rationale noted that comparative safety and HRQoL data were not submitted. The sponsor submitted a cohort study assessing safety and an ITC assessing HRQoL to help fill in the gaps in evidence and provide certainty in the clinical value of teprotumumab versus IVMP.
- The sponsor stated that the 3 RCTs are generalizable to the place in therapy as the only disease-modifying therapy and to clinical practice in Canada.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- new information provided by the sponsor to address an important, clear gap in the evidence identified by CDEC
- feedback from 3 clinical specialists with expertise in diagnosing and treating patients with TED
- feedback on the draft recommendation from 5 patient groups: the Canadian Organization for Rare Disorders, Fighting Blindness Canada — Retina International, the Global Alliance for Patient Access, the TED Community Organization, the Thyroid Foundation of Canada
- feedback on the draft recommendation from 13 clinician groups: Centre hospitalier de l'Université de Montréal; the Kingston Health Sciences Centre TED team; endocrinologists in London, Ontario; oculoplastic surgeons in Manitoba; oculoplastic surgeons in Quebec; oculoplastics fellows in Canada treating patients with TED; ophthalmologists treating patients with TED in the Northwest Territories; TED specialists in Saskatchewan; an ophthalmologist from southwestern Ontario; CSOPS; the Toronto Oculoplastics Society; the University of Alberta Department of Ophthalmology and Visual Sciences; the University of British Columbia TED group
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Initial Meeting Date: March 26, 2025

Members of the committee: Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: March 25, 2026

Members of the committee: Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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