

New Drug Evaluation: Teprotumumab, 500mg, intravenous injection

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Generic Name: Teprotumumab-trbw

Brand Name (Manufacturer): Tepezza® (Horizon Therapeutics, Inc.)

Dossier Received: yes

Research Questions:

1. What is the efficacy of teprotumumab for the treatment of thyroid eye disease?
2. Is there comparative evidence for treatments of thyroid eye disease?
3. Is teprotumumab safe for the treatment of thyroid eye disease?
4. Is there comparative evidence for the safety of drug therapy in patients being treated for thyroid eye disease?
5. Are there sub-populations (based on age, gender, ethnicity, comorbidities, disease duration, or severity) of patients with thyroid eye disease for which teprotumumab is more effective or associated with fewer adverse events?

Conclusions:

- A 2017 phase 2, randomized, double-blind, placebo controlled study assessed the efficacy and safety of teprotumumab versus placebo in the treatment of active thyroid eye disease (TED) associated with Graves' disease (GD).¹ (poor quality)
 - Limitations include a surrogate endpoint for vision loss or surgical need, use of clinical activity score (CAS) as component of primary endpoint, unknown duration of response, lack of targeted applicability based on disease severity, and potentially high selection, detection, reporting, and "other" bias.
- A 2020 phase 3, randomized, double-blind, placebo controlled study assessed the efficacy and safety of teprotumumab versus placebo in the treatment of active, moderate to severe TED associated with GD.² (poor quality)
 - Limitations include a surrogate endpoint for vision loss or surgical need, unknown duration of response, and potentially high detection, reporting, and "other" bias.
- There is moderate quality evidence that teprotumumab showed a greater response rate compared to placebo using a composite endpoint of proptosis reduction of at least 2 mm and CAS reduction of at least 2 points over a period of 24 weeks {[69% vs. 20%; odds ratio (OR) 8.86, 95% confidence interval (CI) 3.29 to 23.8; P<0.001]; absolute risk reduction (ARR) 49%, number needed to treat (NNT) 3]¹[78% vs 7%; difference 72.46%, 95% CI 57.57% to 87.35%; P<0.001; ARR 71%, NNT 2]²].
- There is moderate quality evidence that teprotumumab showed a reduction of proptosis of at least 2 mm compared to placebo over a period of 24 weeks [(Change from baseline -2.46±0.2mm vs -0.15±0.19mm, P<0.001)¹(83% vs. 10%; difference 73%, 95% CI 59% to 88%, p<0.001; ARR 73%, NNT 2)²]
- There is insufficient evidence for safety as fewer than 100 total patients have received this medication. Most common adverse events were muscle spasms (25%), nausea (17%), and alopecia (13%).¹⁻³ Infusion reaction resulted in study discontinuation for one patient.²
- There is insufficient evidence regarding duration of response beyond 24 weeks or for clinical outcomes of vision loss or surgical need.^{1,2}

- There is no evidence regarding place in therapy in relation to current standard of care (pulse corticosteroids) or in patients with sight-threatening disease.^{1,2}
- There is high potential for teratogenicity with fetal exposure to this medication.³

Recommendations:

- Teprotumumab-trbw was designated as non-preferred on the Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan
- Implemented clinical prior authorization for teprotumumab-trbw to ensure appropriate utilization. **(Appendix 2)**

Background:

Hyperthyroidism, caused by an inappropriately high synthesis and secretion of thyroid hormones, is a relatively common condition in the United States (US).⁴ Overt hyperthyroidism affects an estimated 0.5% of adults, while subclinical hyperthyroidism has a prevalence of 0.7%.⁴ Graves' disease is the most common cause of hyperthyroidism and accounts for 50-80% of the cases.⁵ The female to male prevalence of GD is 5:1.⁵

Thyroid eye disease is an inflammatory eye disease of the orbit that develops in conjunction with autoimmune thyroid disorders. It is also known in the medical literature as dysthyroid eye disease, thyroid orbitopathy, thyroid-associated ophthalmopathy, and thyroid-associated orbitopathy. When associated specifically with GD, additional names include Graves' eye disease, Graves' orbitopathy, Graves' ophthalmopathy, and Graves' dysthyroid ophthalmopathy.^{6,7} TED is the result of inflammation in both the orbital connective tissue and extraocular muscles, with eventual fibrosis of the extraocular muscles and adipogenesis within the orbits.⁸ Patient symptoms may include sore, gritty, or red eyes, double vision, reduction of vision, and loss of vision.⁹ Clinical signs include periorbital edema, lid lag, lid retraction, chemosis, exophthalmos, and dysmotility. More severe forms may result in exposure keratopathy, diplopia, and compressive optic neuropathy. Vision loss can occur about 3-7% of those with TED due to corneal exposure (exposure keratopathy) or compressive optic neuropathy (dysthyroid optic neuropathy).^{9,10} Mild cases may still result in significant quality of life (QoL) reductions in affected patients.^{8,9} TED generally follows a biphasic course and is usually self-limiting.^{11,12} There is an 18-36 month active phase with ongoing inflammation accompanied by rapid deterioration, followed by a stable or inactive phase that often results in regression of many signs and symptoms toward baseline, though vision loss may be permanent.^{4,11,12} A group of 59 patients with TED who had never received medical or surgical treatment for eye disease at presentation to a specialty thyroid-eye clinic were then followed for a median of 12 months to study the natural disease course; 22.0% improved substantially, 42.4% showed minor improvement, 22% were unchanged, and 13.5% continued to deteriorate necessitating immunosuppressant treatment.¹³

Roughly 90% of TED cases are in patients with current or a history of GD. Other thyroid disorders, such as Hashimoto's thyroiditis, an autoimmune condition generally resulting in hypothyroidism, also have been associated with TED. Severity is usually classified as sight-threatening, moderate to severe, and mild.¹¹ Symptomatic TED develops in roughly 30-50% of patients with GD,^{4,8,9} though magnetic resonance imaging (MRI) or computed topography (CT) have shown extraocular muscle enlargement in as many as 70% of patients.⁸ Only 5% of patients with GD go on to develop moderate or severe TED.⁴ Smoking increases risk of developing TED by 7 to 8 fold,¹⁰ as well as the severity of TED, particularly after radioactive iodine (RAI) therapy for hyperthyroidism.¹¹ There is a demonstrated dose-response relationship to number of cigarettes/day and likelihood of TED development. Continued smoking may hinder the effectiveness of historical treatments such as corticosteroids, though data are lacking for if this remains true with newer therapies.^{4,11} Women are more likely to develop GD and men may be at higher risk of developing severe TED. However, the sex-related risk is unclear and may be associated with historical population tobacco-use patterns.⁴ More severe cases of TED are generally seen in elderly patients.⁴ Incidence peaks during the 5th and 6th decades of life with a median age at diagnosis of 43 years.^{4,10} Incidence rates of 16/100,000 in women and 2.9/100,000 in men, with an overall calculated prevalence of 0.25% have been reported.⁹ Additional risk factors included for TED development in the setting of GD are RAI use for definitive treatment of hyperthyroidism, untreated hyperthyroidism, and post-

treatment hypothyroidism.⁴ Most patients with active TED at time of RAI receive prophylactic oral corticosteroids (CS) beginning 1-3 days post-RAI dosed at 0.4-0.5 mg/kg/day prednisone equivalent for one month, then tapered over 2 months, to prevent TED progression.⁴ Thyroid-stimulating hormone receptor autoantibodies are also an independent risk factor for severity and progression of TED.¹² A family history of TED is present in 61% of TED patients.¹⁰ In patients who receive surgical treatment for GD, total thyroidectomy is more effective at preventing recurrent hyperthyroidism than subtotal thyroidectomy (including both bilateral subtotal thyroidectomy and the Dunhill procedure). However, surgery type does not affect regression of TED.⁵ Antithyroid medications (e.g. methimazole, propylthiouracil) may be used to manage hyperthyroidism without affecting the disease course of TED.¹¹

Sight-threatening disease with dysthyroid optic neuropathy should be treated with intravenous (IV) CS, followed by surgical decompression if there are CS contraindications or no response to IV CS therapy after 1-2 weeks.¹¹ Moderate to severe disease is currently managed with IV CS with or without orbital radiotherapy.^{6,11} Orbital inflammation is reduced by IV CS in 50-80% of treated patients with moderate-severe TED, though there is an estimated 11% relapse rate at 12 weeks.¹⁴ Sight-threatening corneal breakdown is addressed with aggressive topical lubrication and consideration for CS or surgery when lubricants are ineffective. Patients with moderate to severe active TED should receive IV CS pulses, with consideration for orbital radiotherapy in patients with diplopia or restricted motility who lack contraindications (e.g. diabetic retinopathy, severe hypertension).¹¹ Oral steroids generally have a total daily dose of 80-100 mg prednisone (~1 mg/kg) and are tapered over 2-3 months.¹¹ IV CS have multiple studied dosing regimens including 15 mg/kg infusions for 4 cycles with each cycle being two infusions on alternate days at 2 week intervals, followed by 7.5 mg/kg for an additional 4 cycles for a total dose of 9-12 grams; this regimen was used following RAI.¹⁵ Alternatively, 500 mg IV methylprednisolone daily for 3 days each week for 4 weeks has also been used.¹⁶ The use of IV CS is considered more effective than oral CS based on two studies which show response rates of 77-88% for IV CS (± radiotherapy) compared to 51-63% for oral CS (± radiotherapy).¹¹ Disease can flare when tapering or discontinuing steroids.¹¹ The use of CS in mild TED is rarely appropriate.¹¹ Other therapies have been studied in TED, but none have high-quality data supporting their use.^{9,14} A 2018 Cochrane review of tocilizumab in TED found no studies that met their inclusion criteria.⁹ An older Cochrane review on rituximab also found no acceptable studies, but three more recent publications have shown mixed results.^{8,17-19} These prospective, randomized studies include: no difference versus placebo, statistical improvement from baseline with rituximab + RAI similar to the improvement of CS + RAI, and statistical superiority of rituximab at week 24 compared CS.¹⁷⁻¹⁹ Additional immunosuppressants that have been studied in the literature include mycophenolate mofetil, azathioprine, cyclosporine, and methotrexate.¹⁴ Additional therapies which have been studied include somatostatin analogs, botulinum toxin (for upper lid retraction), and selenium supplementation.^{4,11} None of these medications hold Food and Drug Administration (FDA) approvals for usage in TED and the data for their use remains mixed, though rituximab, tocilizumab, and mycophenolate mofetil have shown the most potential.¹⁴

There are several scales and classification systems used to describe thyroid eye disease as the understanding of this disease has developed over time. The disease is characterized by both *severity* and if it is *active* or *inactive*. The NO SPECS Classification (also called Werner's classification system) was first introduced in 1969 and modified in 1977 and refers to no physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular involvement, corneal involvement, and sight loss due to optic nerve involvement; though it is less utilized than other classification modalities currently available today it was used in many older studies to evaluate efficacy.⁹ This classification system grades clinical severity, but does not differentiate between inflammatory progressive and non-inflammatory status.

The American Thyroid Association (ATA) recommends the severity assessment seen in **Table 1** for Graves' orbitopathy.^{4,9} The European Group of Graves' Orbitopathy (EUGOGO) defines severity similarly, though moderate to severe is a combined category of severity (**Table 2**).¹¹

The Clinical Activity Score (CAS) is commonly used and it differentiates active from non-active forms of TED (**Table 3**). The 10-point (10 item) version requires 2 clinical examinations as 3 items reflect change in clinical signs. A score of 3 of 7 at first examination or 4 of 10 after repeat examination indicates active disease,

though a score of at least 4 of 7 has been required in some medication trials.⁹ The EUGOGO modified this scoring to only use the 7 items that do not require repeat examination, and exclude change in visual acuity, diplopia, or proptosis.⁹ CAS was originally validated based on its ability to correctly predict response to 12 weeks of tapered oral prednisone or orbital radiotherapy treatment, in 43 patients with moderate to severe Graves’ ophthalmopathy.²⁰ These patients were 20-75 years old and had been euthyroid for at least 3 months.²⁰ This validation study determined that a CAS at least 4 of 7 on the initial assessment had a sensitivity of 55% and specificity of 86%. With an assumed 35% non-response rate, this led to a positive predictive value of 80% and negative predictive value of 64% of a change of at least one NO SPECS class.²⁰ It is important to note that increased sympathetic state caused by hyperthyroidism can result in lid retraction or stare. When these are present without associated eye changes they are not thought to be part of TED and should be scored as absent on CAS.⁴

An additional classification known as the VISA Classification (vision, inflammation, strabismus, and appearance/exposure) is used to assess both severity and activity, and is often used in the United States (US), though less often in Europe.^{9,12} Each of the 4 inputs has multiple severity parameters and it is graded independently, with a maximum possible score of 20.¹² The inflammatory input component of VISA has a maximum score of 10, with 4 or less considered moderate and 5 or above considered severe.¹² The EUGOGO Classification uses the CAS as to evaluate activity, while severity are compared to an image atlas developed by the group.^{11,12}

EUGOGO has specific severity measures recommended during patient assessment.^{11,21} The Clinical Measures of Severity Score (CSS) is based on these severity measures. Each CSS item should be considered an individual parameter, as there is no overall score and use of this tool in literature was just introduced in studies evaluated below.^{11,21,22}

EUGOGO has developed several QoL tools including Graves’ orbitopathy (GO) quality of life questionnaire (GO-QOL), GO quality of life scale (GO-QLS), and TED quality of life questionnaire (TED-QOL).¹² These have shown moderate correlation to disease severity.¹² The GO-QOL includes a visual functioning subscale (score 0-100) and an appearance subscale (score 0-100), these can be assessed independently or in combination (overall score range 0-100).

EUGOGO has made recommendations for minimum changes to objective parameters for assessing response in clinical trials.²¹ These include a CAS change of ≥ 2 , proptosis change of ≥ 2 mm, and subjective diplopia change of at least 1 grade. For subjective parameters, the GO-QOL is considered valid and a ≥ 6 point change on either subscale is considered meaningful, though an overall minimum score change was not explicitly defined.²¹ The FDA considers a 2 mm reduction in proptosis clinically meaningful as it is expected to reduce diplopia and improve corneal lid coverage.¹⁰ The FDA has not been provided with validation information on the GO-QOL and therefore does not currently include results interpretation in drug reviews.¹⁰ Furthermore, changes in CAS are not accepted by the FDA as an appropriate measurement of response as “there is not necessarily equal weight for each component”.¹⁰

Table 1: Graves’ Orbitopathy Severity Assessment⁴

Grade	Lid retraction	Soft tissues	Proptosis*	Diplopia	Corneal exposure	Optic nerve status
Mild	< 2 mm	Mild involvement	< 3 mm	Transient or absent	Absent	Normal
Moderate	2 mm	Moderate involvement	3 mm	Inconstant	Mild	Normal
Severe	2 mm	Severe involvement	3 mm	Constant	Mild	Normal
Sight threatening	-	-	-	-	Severe	Compression

Abbreviations: F/M = female/male; mm = millimeter

* Variation compared to upper limit of normal for race/sex or the patient’s baseline (if available)

Table 2: EUGOGO Disease Severity for Graves' Orbitopathy²¹

Severity	Specific signs/symptoms	General Management
Mild	Typically one or more of following: minor lid retraction ≤ 2 mm, mild soft tissue involvement, exophthalmos < 3 mm above normal for race and gender, transient or no diplopia, corneal exposure responsive to lubricants.	<ul style="list-style-type: none"> • Minor impact on daily life • Disease not sufficient to justify immunosuppressive or surgical treatment
Moderate to Severe	Typically one or more of following: Lid retraction ≥ 2 mm, moderate-severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, inconstant or constant diplopia	<ul style="list-style-type: none"> • Not sight threatening • Disease has sufficient impact on daily life to justify immunosuppression (active disease) or surgical intervention (inactive disease)
Sight threatening	Dysthyroid optic neuropathy and/or corneal breakdown	<ul style="list-style-type: none"> • Immediate intervention needed

Table 3: Clinical Activity Score^{4,12}

Elements	Each visit	Comparison with previous visit	Score
Painful feeling behind the globe over last 4 weeks	X		1
Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (flesh body at medial angle of the eye) <i>and/or plica*</i>	X		1
Increase in proptosis greater than or equal to 2 mm		X	1
Decreased eye movements greater than or equal to 5° (<i>or greater than or equal to 8°</i>)* in any direction		X	1
Decreased visual acuity greater than or equal to 1 line on Snellen chart		X	1

* Modifications for EUGOGO CAS in italics

Teprotumumab was approved in January 2020 as an orphan drug for the treatment of thyroid eye disease.³

As of October 2020, there has not been any previous usage of teprotumumab in the OHP fee-for-service (FFS) population. It is estimated that fewer than 20 patients are currently receiving corticosteroids or off-label immunosuppressant therapies for TED. Approximately 450 FFS OHP patients have had claims related to Graves' disease in 4th quarter 2019 through 1st quarter 2020, leading to an estimated 23 patients with moderate-severe TED using a 5% historical incidence rate. Given that the risk of severe TED increases with age and that not all patients may be in the active phase of disease, this may be an overestimation in the Medicaid population.

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Teprotumumab is a first in class insulin-like growth factor-1 receptor inhibitor (IGF-1R). It is approved for use in TED, though details of its mechanism of improvement are not fully characterized.³

The efficacy and safety of teprotumumab was evaluated in a phase 2, randomized, placebo-controlled, double-masked trial (NCT01868997).^{1,10,22,23} Participants were randomized using an interactive web response system and stratified by smoking status at each site to receive teprotumumab infusions (n=42) of 10 mg/kg initially, followed by 20 mg/kg or matching placebo infusions (n=45) every 3 weeks for 24 weeks, then a 48 week follow up period (n=39 post-teprotumumab, n=36 post-placebo).^{1,22} Patients had a history of GD and active TED, defined as a CAS of at least 4, and ophthalmic symptoms for no more than 9 months prior to enrollment.^{1,22} Patients were initially included if euthyroid and stable on at least 2 months of antithyroid medication or with a history of RAI or surgical thyroidectomy.²² This was amended early in recruitment to euthyroid with excursions of free triiodothyronine (T3) and free thyroxine (T4) allowed to no more than 50% above or below normal levels; there was no specific requirement for underlying treatment of GD.²² Previous medical or surgical treatment for TED was not allowed, except up to 1 gram of oral methylprednisolone equivalent with a 6 week washout.^{1,22} See Table 6 for additional inclusion and exclusion criteria.

The study began in July 2013 and had a primary completion date of March 2016.²⁴ The primary and secondary endpoints, assessed at week 24, were amended in Sept 2015.²² The authors report that there was no interim data analysis.¹ The primary endpoint assessed difference in rate of response to treatment and initially defined a “responder” as a patient with a CAS decrease of ≥ 2 points or improvement in ductions of ≥ 10 degrees or a reduction of proptosis of ≥ 2 mm with no deterioration in non-study eye.²² This was altered to a composite endpoint where a responder required both CAS and proptosis improvements while having no deterioration of the non-study eye.²² Mobility restriction was removed as a measure in the primary and secondary endpoints. Final secondary endpoints were reported as GO-QOL, proptosis, and CAS.²² Mobility restriction, time to response, and CSS were changed to exploratory endpoints.^{1,22,23}

Participants had an average age of 52.9 years and were primarily female (73.6%) and White (86.2%). The teprotumumab group had a statistically significantly higher response rate when compared to placebo at week 24 [69% vs. 20%; OR 8.86, 95% confidence interval (CI) 3.29 to 23.8; $P < 0.001$] in the intention to treat (ITT) population.¹ Change in proptosis from baseline for teprotumumab (-2.46 ± 0.20 mm) versus placebo (-0.15 ± 0.19 mm) was also statistically significant ($P < 0.001$), as was change in CAS for teprotumumab (-3.43 ± 0.18) versus placebo (-1.85 ± 0.17 ; $P < 0.001$).¹ The QOL assessments found statistically significant difference Overall (teprotumumab 17.7 ± 2.4 vs. placebo 6.8 ± 2.3 ; $P < 0.01$) and in the Visual-functioning subscale (teprotumumab 21.7 ± 2.9 vs. placebo 7.5 ± 2.7 ; $P < 0.001$), but not the Appearance subscale (teprotumumab 12.9 ± 2.8 vs. placebo 6.6 ± 2.7 ; $P = 0.10$).¹

This study met the primary endpoint, however, until publication of data of the follow-up period of this study, the duration of response is unknown. There is concern for relapse given the active period of up to 36 months during the disease course of TED (see “other relevant outcomes” from follow-up period, **Table 6**).¹⁰ Longer term data may also elucidate if this therapy is effective for the clinical goal of reduction of vision loss due to TED. There is possible selection bias between groups. Despite stratification, only 26% of teprotumumab patients compared to 41% of placebo patients were smokers; the authors had anticipated approximately 50% of participants would be smokers.^{1,22} There was also imbalance in the free T3 and free T4 levels between groups. More teprotumumab (46%) versus placebo (30%) patients were euthyroid at baseline, and this continued when comparing values occasionally out of normal range (teprotumumab 42% vs. placebo 57%), though groups were similar for values sustained out of range (teprotumumab 12% vs. placebo 14%).^{1,23} Untreated hyperthyroidism and post-

treatment hypothyroidism are TED risk factors.⁴ Additionally, sympathetic activation from hyperthyroidism can result in eye changes such as lid retraction and stare, which can hinder accurate CAS scoring.⁴ There is concern whether previous thyroid treatment was accurately recorded as 62% of teprotumumab patients and 59% of placebo patients were receiving levothyroxine or thyroid extract at baseline¹ while only 22.7% and 23.2% from each group were reported to have had previous RAI or surgical thyroidectomy.²³ Also, three patients received the wrong treatment.¹⁰ It is unclear if the amended endpoints introduce reporting bias as the updated primary endpoint appears more stringent. Ophthalmic assessments were performed by the same clinician throughout the study period with each patient when possible. Although this method may have increased efficiency and consistency, this continuity could possibly have led to unblinding for patients in the treatment group with a notable early proptosis response and detection bias in subjective variables such as components of the CAS. Detection bias may explain the large difference in responder rates between groups and overall low placebo responder rate, particularly given that TED is often self-limiting and has been shown to improve to some extent in more than 50% of patients without treatment over a 12 month period.¹³ Targeted applicability is limited by omission of severity rating from inclusion criteria^{1,10,22} as TED should be categorized by activity and severity.⁴ This omission also complicates placement in therapy; current therapies of pulse steroids, surgery, and orbital radiotherapy are used in relation to severity during active disease. Baseline reporting of severity would have been appropriate for group comparison as well. There is additional potential bias due to industry involvement in trial design, funding, and oversight. Overall this trial is judged to be of poor quality due to risk of bias.

Teprotumumab was evaluated in a second study, a phase 3, randomized, placebo-controlled, double-masked trial (NCT03298867).^{2,10,25,26} The randomization process and drug intervention were the same as the previously described study.^{2,25} Inclusion and exclusion criteria were similar, though with the important addition that patients were required to have moderate to severe TED as defined by parameters consistent with the Graves' Orbitopathy Severity Assessment.^{2,25} There were 41 patients in the teprotumumab group and 42 who were randomized to receive placebo. Patients had an average age of 50.2 years and were primarily female (72.3 %) and White (86.7%).

A proptosis reduction of ≥ 2 mm at week 24 was the primary endpoint and 83% of teprotumumab patients and 10% of placebo patients achieved this response (difference 73%, 95% CI 59% to 88%, $p < 0.001$).² Teprotumumab was statistically superior to placebo in all secondary endpoints as well (**Table 6**), including combined proptosis response and CAS reduction of ≥ 2 points at week 24 (teprotumumab 78% vs. placebo 7%, difference 71%, 95% CI 56% to 86%, $p < 0.001$).² Diplopia was added as a secondary endpoint via amendment on Jan 31st, 2019, just prior to the primary study completion date of Feb 13th, 2019.^{25,27}

The baseline patient characteristics of the groups in this study were well balanced including smoking status, though previous history of thyroid treatment (specifically RAI) was not reported and thyroid hormone levels were only presented as mean and median values with ranges. Quality of thyroid control as described by time within range between the groups was unable to be evaluated. The reported duration of GD was very different in the two studies, with a mean of 10.7-10.8 months in the Smith et al study, but a mean of 2.2-3.5 years in the Douglas et al study, though it is unclear if this has any clinical significance.^{1,2} This study also used the same clinician to perform the ophthalmic evaluations and is subject to the same potential detection bias. The extreme differences in the treatment and placebo group are again notable, with only 7% placebo response to the composite secondary endpoint (compared with 20% placebo response in the initial study), despite the natural disease course of TED and less than half of the smoking rate compared to the placebo group in the initial study. Data from the follow-up period regarding duration of effect are not currently available. There is potential for reporting bias due to the amended secondary endpoint, and other bias from industry involvement as well. This trial is also judged to be of poor quality due to risk of bias.

In summary, teprotumumab is a newly approved agent for TED which has shown moderate quality of evidence for reduction of proptosis of at least 2 mm and for a composite endpoint of response using proptosis reduction of at least 2 mm and CAS reduction of at least 2 points when compared to placebo in patients with active, moderate to severe TED after 24 weeks. Evidence was demoted due to multiple methodologic sources of potential bias creating an overall high risk

of bias (**Table 6**) and promoted due to large magnitude of effect with consistency between studies. The FDA does not recognize the CAS scale as an appropriate primary endpoint measure.¹⁰ There is insufficient evidence regarding duration of response beyond 24 weeks, clinical outcomes of vision loss and surgical need, and for safety. There is no evidence regarding place in therapy in relation to current standard of care (pulse corticosteroids) or in patients with sight-threatening disease.

Clinical Safety:

Labeled clinical warnings for teprotumumab include infusion reactions, exacerbation of irritable bowel disease (IBD), and hyperglycemia. Most adverse effects (AE) in the studies were mild in severity. AEs are found in **Table 4**. Infusion reactions, generally mild or moderate, may occur at any time during and up to 1.5 hours after any infusion. One patient discontinued treatment after infusion reaction.² After a reaction, subsequent infusions can include premedication with an antihistamine, antipyretic, CS, and/or a slower medication infusion rate.³ Patients with preexisting IBD should be monitored for flare. Clinicians should consider teprotumumab discontinuation if an IBD exacerbation occurs. Hyperglycemia was seen in 10% of teprotumumab treated patients, with two-thirds of these patients reporting preexisting diabetes.³ Blood glucose should be monitored throughout treatment and patients with preexisting diabetes should be controlled prior to initiation of teprotumumab.³ Modification of medications may be needed during treatment to regain glycemic control in diabetic patients.¹

Teprotumumab is highly suspected to result in fetal harm due to evidence from animal based studies and its mechanistic inhibition of IGF-1R.³ Exposure in pregnant monkeys resulted in external and skeletal abnormalities.³ Appropriate contraception should be initiated prior to treatment, during treatment, and for six months after final dose of teprotumumab.³ Drug discontinuation should occur in the event of pregnancy.³ Both study protocols were amended to refine definitions of appropriate contraception, duration of contraception after last study dose, and increase frequency of pregnancy monitoring throughout the active study periods.^{22,25} The final inclusion criteria for the Douglas et al. study included pregnancy tests at baseline and all study visits through week 48 for women of childbearing potential (those with onset of menopause for less than 2 years or non-therapy-induced amenorrhea for less than 12 months before screening, and not surgically sterile).²⁵ Additionally, those female participants of childbearing potential who were sexually active with a non-vasectomized male partner were required to use 2 reliable forms of contraception (defined as those with failure rates of <1%) with hormonal contraception recommended as one of those two types for all patients, and initiated one full cycle before the first study infusion and continued for 180 days after the final study infusion.²⁵ Non-vasectomized male subjects, who were sexually active with a female partner of childbearing potential, agreed to the use of barrier contraceptives from screening until 180 days after the final study infusion.²⁵

Table 4. Treatment Emergent Adverse Events³

Adverse Reactions	Teprotumumab N=84 N (%)	Placebo N=86 N (%)
Muscle Spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue	10 (12%)	6 (7%)
Hyperglycemia	8 (10%)	1 (1%)
Hearing Impairment	8 (10%)	0

Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry Skin	7 (8%)	0

* Numbers differ from Table 6 due to receipt of study drug by placebo patient.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Reduction of TED complications (including vision loss, need for surgery, need for orbital irradiation)
- 2) Change in Severity of TED
- 3) Improved Quality of Life
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Composite reduction of proptosis and CAS¹
- 2) Reduction of proptosis²

Table 5. Pharmacology and Pharmacokinetic Properties³

Parameter	
Mechanism of Action	<ul style="list-style-type: none"> • Binds to IGF-1R, blocking activation and signaling • Mechanism of action in thyroid eye disease not fully characterized
Oral Bioavailability	N/A
Distribution and Protein Binding	<ul style="list-style-type: none"> • 3.26 ± 0.87 L central VD, 4.32 ± 0.67 L peripherally • Protein binding not reported
Elimination	NR
Half-Life	<ul style="list-style-type: none"> • 20 ± 5 days • no clinically significant differences based on age (18-80 y), gender, race/ethnicity (103 White, 10 Black, 3 Asian), weight (46-169 kg), renal impairment (mild-moderate using Cockcroft-Gault equation), bilirubin level (2.7-24.3 mcmol/L), AST level (11-221 unit/L), ALT level (7-174 unit/L) • Effect of hepatic impairment unknown
Metabolism	Not fully characterized, anticipated to undergo proteolysis

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; IGF-1R = insulin-like growth factor- 1 receptor; L = liter; mcmol= micromole; N/A = not applicable; NR = not reported; VD = volume of distribution; y = years

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. NCT01868997 1,10,22,23 Smith et al. Phase 2, DB, PC, MC, RCT	1. Placebo (normal saline) IV infusion q3wk over 24 wk for 8 total doses 2. Teprotumumab 10 mg/kg IV infusion x 1, then 20 mg/kg IV infusion q3wk x 7 1:1 randomization Study timeline -Screening (2-6 weeks): 1-3 visits -Intervention (24 weeks-used for primary/secondary endpoints): every 3 weeks -Follow-up (48 weeks): every 12 weeks, no additional treatment for at least initial 12 weeks.	<u>Demographics:</u> -Mean age: PCB 54.2±13.0y Tep 51.6±10.6y -Age >= 65 y: PCB 20% TEP 9% -Female: PCB: 82% TEP: 65% White: 86% Smoker: PCB 41% TEP 26% -Mean duration of GD: PCB 10.8m (1.2-299.0) TEP 10.7m (1.2-228.0) -Median time since thyroid tx initiation: PCB 15m (3-189) TEP 8m (1-134) -Mean duration eye symptoms: PCB 5.2±2.3m TEP 4.7±2.1m <u>Key Inclusion Criteria:</u> - 18 to 75 y old - Clinical dx of GD with active TED with CAS ≥ 4 in more severely affected eye - TED dx ≤ 9 months after onset of symptoms* - Euthyroid (± 50% reference range FT3 and FT4) * - no hx surgical or medical tx (ex. oral methylprednisolone equivalent ≤ 1 g cumulative, 6 wk washout)* -Not requiring immediate ophthalmological surgical intervention	<u>ITT:</u> 1. 45 2. 42 <u>PP:</u> 1. 36 2. 33 <u>Safety:</u> 1. 44 2. 43 <u>Attrition:</u> 1. 6 (13.3%) 2. 5 (11.9%)	<u>Primary Endpoint:*</u> Responder rate: CAS decrease ≥2 AND Proptosis decrease ≥ 2mm AND no worsening of non-study eye <u>ITT:</u> 1. 9/45 (20%) 2. 29/42 (69%) OR 8.86 (95% CI 3.29 to 23.8) P <0.001 <u>Secondary Endpoints:*</u> Change from Baseline Proptosis (mm) 1. -0.15 ± 0.19 2. -2.46 ± 0.20 P<0.001 CAS (7 point scale) 1. -1.85 ± 0.17 2. -3.43 ± 0.18 P<0.001 GO-QOL (100 point scale overall and each subscale)† Overall 1. 6.8 ± 2.3 2. 17.7 ± 2.4 P < 0.01 Visual functioning subscale 1. 7.5 ± 2.7 2. 21.7 ± 2.9 P <0.001 Appearance subscale 1. 6.6 ± 2.7 2. 12.9 ± 2.8 P=0.10	49%/3 NA NA NA	<u>Outcome:</u> Death 1. 0 2. 0 Discontinuation: 1. 6 2. 6 Serious AE: 1. 1 (2%) 2. 5 (12%) Any AE 1. 32 (73%) 2. 32 (74%)	10%/10	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (High) Randomized 1:1 and stratified at each site and smoking status by an interactive web-response system. Significant group imbalances of important variables noted: including; sex, smoking (<i>despite stratification</i>), thyroid hormone levels, and time since thyroid tx initiation. Unclear quality of baseline variable assessment [ex. incongruence between history of RAI or surgical thyroidectomy (23%) and those on thyroid replacement (61%); median time since thyroid tx initiation longer than mean duration of GD]. Allocation concealment not described. <u>Performance Bias:</u> (Low) Patients, investigators, and trial-site personnel were blinded. Method to maintain blinding not described. Dispensing pharmacists were aware of group assignment and dispensed matched placebo. <u>Detection Bias:</u> (High) Same clinician measured outcomes at each visit for individual patients when possible. Investigators provided training and copies of same resource for CAS for consistency across trial sites. Unclear if proptosis effect may contribute to unblinding and effect size of subjective CAS measures given continuity created by using same observer. GO-QOL was self-administered. <u>Attrition Bias:</u> (Low) Intention to treat analysis used, dropout > 10% but similar between groups. Week 24 data included for all patients, including discontinuations. If week 24 data unavailable, patient was considered to have failed treatment for binary outcomes. No imputation of missing data for secondary endpoints as MMRM model accommodates missing data. <u>Reporting Bias:</u> (High) Significant protocol changes of endpoints near end of study period, though no interim data analysis is reported to have been done. Over emphasis of exploratory

		<p>-DM controlled by no change medication or insulin >10% in previous 60 days</p> <p>-Neg. pregnancy tests and stringent birth control for women of childbearing potential and men in protocol and 90 days after final study drug administration. See protocol for details*</p> <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> - optic neuropathy - severe ocular surface damage - CAS 2 or more point improvement b/t screening and baseline visit -Treatment with oral or IV steroids in previous 3 months except as above. Administration of any other immunosuppressive agent for any indication in the previous 3 months other than topical steroids for dermatologic use* - Previous treatment with rituximab - Hx orbital irradiation 		<p><u>Other relevant outcomes</u>¹⁰:</p> <p>Follow-up period additional therapy with pulse corticosteroids ± rituximab ± orbital decompression</p> <ol style="list-style-type: none"> 1. 6 (0/6 responders at week 24) 2. 4 (4/4 responders at week 24) <p>Proptosis relapse ≥2 mm in responders week 24 to 72</p> <ol style="list-style-type: none"> 1. 3/9 2. 11/30 <p>(1/30 TEP had missing value as had orbital decompression at week 70)</p>			<p>endpoints (i.e., onset of response, time course, graded response, patients with CAS of 0 to 1).</p> <p><u>Other Bias:</u> (High) Manufacturer (River Vision Development, later acquired by Horizon Pharmaceuticals) collaborated on trial design, provided funding, and was responsible for trial oversight. Multiple protocol changes involving important inclusion/exclusion criteria such as clarification of previous steroid medication use and current thyroid status throughout study period.</p> <p><u>Applicability:</u></p> <p><u>Patient:</u> Absence of baseline severity limits understanding of patient population treated. Patient population of primarily white patients may not accurately represent Medicaid population or general disease distribution. No data on non-GD induced TED, those with previous treatment with failure, incomplete response, or relapse after steroid or other immunosuppressant, or those with sight-threatening disease.</p> <p><u>Intervention:</u> Dose based on previous oncology dose ranging studies. Inadequate data on repeat dosing, concomitant steroid use, and duration of effects to understand long term benefit.</p> <p><u>Comparator:</u> Placebo; active comparator against current standard of care (i.e. corticosteroids) lacking</p> <p><u>Outcomes:</u> Composite containing CAS response (with proptosis response) not considered appropriate by FDA. Proptosis appropriate surrogate. Not designed to study long term reduction of TED induced vision loss. Questions remain from FDA regarding validity of GO-QOL.</p> <p><u>Setting:</u> 15 sites in US and Western Europe</p>
<p>2. OPTIC</p> <p>NCT 03298867^{2,10,25,26}</p>	<p>1. Placebo (normal saline) IV infusion q3wk over 24 wk for 8 total doses</p> <p>2. Teprotumumab 10 mg/kg IV</p>	<p><u>Demographics:</u></p> <ul style="list-style-type: none"> -Mean age: PCB 48.9±13.0y TEP 51.6±12.6y -Age ≥/= 65 y: PCB 10% TEP 22% 	<p><u>ITT:</u></p> <ol style="list-style-type: none"> 1. 42 2. 41 <p><u>PP:</u></p> <ol style="list-style-type: none"> 1. 34 2. 33 	<p><u>Primary Endpoint:</u></p> <p>Proptosis responder rate: Proptosis ≥ 2mm reduction from baseline</p> <p><u>ITT:</u></p> <ol style="list-style-type: none"> 1. 10% 2. 83% 	<p>73%/2</p>	<p><u>Outcome:</u></p> <p>Death</p> <ol style="list-style-type: none"> 1. 0 2. 0 <p>Discontinuation:</p> <ol style="list-style-type: none"> 1. 1 	<p>Risk of Bias (low/high/unclear):</p> <p><u>Selection Bias:</u> (Low) Randomized 1:1 and stratified by tobacco status using interactive web response system. Study groups well balanced. Method of allocation concealment not described. Baseline groups similar.</p>

<p>Douglas et al.</p> <p>Phase 3, DB, PC, MC, RCT</p>	<p>infusion x 1, then 20 mg/kg IV infusion q3wk x 7</p> <p>1:1 randomization</p> <p>Study timeline</p> <p><u>-Screening:</u> 2-6 weeks prior to baseline</p> <p><u>-Intervention</u> (24 weeks-used for primary/secondary endpoints): every 3 weeks</p> <p><u>-Follow-up</u> (48 weeks): proptosis responders every 12 weeks, no additional treatment for at least initial 12 weeks.</p> <p><u>-Open-label extension study/NCT03461211:</u> (48 weeks): proptosis non-responders or responders who relapse from either study group may receive 8 drug infusions as above with additional follow-up.</p>	<p>-Female: PCB: 74% TEP: 71% White: 87%</p> <p>Smoker (current or former): PCB 19% TEP 22%</p> <p>-Mean duration of GD: PCB 2.2±3.2y TEP 3.5±6.1y</p> <p>-Mean duration TED PCB 6.4±2.4m TEP 6.2±2.3m</p> <p><u>Key Inclusion Criteria:</u></p> <p>-18 to 75 y old</p> <p>- Dx of GD</p> <p>-Active, moderate-to-severe TED</p> <p>-CAS ≥ 4 in more severely affected eye</p> <p>- ≤ 9 months after onset of ocular symptoms</p> <p>- Euthyroid (± 50% reference range FT3 and FT4)</p> <p>-Not requiring immediate ophthalmological surgical intervention</p> <p>-DM patients must be controlled by having no new medication or change medication or insulin >10% in previous 60 days AND HbA1C <9.0%</p> <p>-Neg. pregnancy tests and stringent birth control requirements for women of childbearing potential and men throughout protocol and 90 days after final study drug administration. See protocol for details.</p> <p><u>Key Exclusion Criteria:</u></p> <p>-optic neuropathy</p>	<p><u>Safety:</u></p> <p>1. 42 2. 41</p> <p><u>Attrition:</u></p> <p>1. 2 (4.8%) 2. 2 (4.9%)</p>	<p>Treatment difference 73.45% (95% CI 59% to 88%) P <0.001</p> <p><u>Secondary Endpoints:</u></p> <p>Overall responder rate: CAS decrease ≥2 AND Proptosis decrease ≥ 2mm AND no worsening of non-study eye</p> <p>1. 7% 2. 78%</p> <p>Treatment difference 72.46% (95% CI 57.57% to 87.35%) P<0.001</p> <p>CAS value 0 or 1 (7 point scale):</p> <p>1. 21% 2. 59%</p> <p>Treatment difference 36.03% (95% CI 17.39% to 54.67%) P<0.001</p> <p>LS Mean change in measurement of proptosis from baseline:[‡]</p> <p>1. -0.53mm 2. -3.32mm</p> <p>Treatment difference -2.79mm (95% CI -3.4mm to -2.17 mm) P NR</p> <p>GO-QOL (100 point scale overall and each subscale):</p> <p>1. 1.80 2. 17.28</p> <p>Treatment difference 15.48 (95% CI 8.43 to 22.53) P NR</p> <p>Diplopia responder rate at wk 24:*</p> <p>1. 29% (8/28) 2. 68% (19/28)</p> <p>Difference 39% (95% CI 16% to 63%) P=0.001</p>	<p>71%/2</p> <p>38%/3</p> <p>NA</p> <p>NA</p>	<p>2. 1</p> <p>Serious AE: 1. 1 2. 2</p> <p>Any AE 1. 29 (69%) 2. 35 (85%)</p>	<p>16%/7</p>	<p><u>Performance Bias:</u> (Low) Patients, investigators, and trial-site personnel were blinded. Method to maintain blinding not described. Dispensing pharmacists were aware of group assignment and dispensed matched placebo.</p> <p><u>Detection Bias:</u> (High) Same clinician measured outcomes at each visit for individual patients when possible. Investigators provided training and copies of same resource for CAS for consistency across trial sites. Unclear if proptosis effect may contribute to unblinding and effect size of subjective CAS measures given continuity created by using same observer. GO-QOL was self-administered.</p> <p><u>Attrition Bias:</u> (Low) Intention to treat analysis and low dropout (<5%). Week 24 data included for all patients, including discontinuations. If week 24 data unavailable, patient was considered to have failed treatment for binary outcomes. No imputation of missing data for proptosis and GO-QOL as MMRM model accommodates missing data.</p> <p><u>Reporting Bias:</u> (High) Primary and secondary endpoints all reported. Secondary endpoint of diplopia response added by amendment just prior to study completion. No interim data analysis was planned. LS mean average change in proptosis results differed in study publication and FDA review document. Thyroid status reported as group means rather than percentage of patients inside or outside of range, therefore unable to compare level of control between groups & between studies.</p> <p><u>Other Bias:</u> (High) Manufacturer (Horizon Therapeutics) sponsored trial, designed with input from investigator steering committee, contributed in collection, analysis, and interpretation of data, and in manuscript creation. Trial was conducted with oversight from a contract research organization (Syneos Health).</p> <p><u>Applicability:</u></p> <p><u>Patient:</u> Patient population of primarily white patients may not accurately represent Medicaid population or general disease</p>
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		<ul style="list-style-type: none"> -corneal decompensation unresponsive to medical management - Improvement of CAS by 2 or more points or proptosis by 2 mm b/t screening and baseline visit - Hx orbital irradiation -TED treatment with oral steroid cumulative dose \geq 1 g methylprednisolone equivalent; < 1 g methylprednisolone equivalent cumulative dose requires 6 wk washout -Oral steroid use for any indication other than TED in the previous 3 months other than topical steroids for dermatologic use -Selenium or biotin use other than in multivitamin, must be d/c 3 weeks prior to screening - Previous treatment with rituximab or tocilizumab -Other immunosuppressive agent within 3 months of screening -Biopsy-proven or clinically suspected inflammatory bowel disease 						<p>distribution. Inclusion of baseline severity appropriate for study drug. No data on non-GD induced TED, those with previous treatment with failure, incomplete response, or relapse after steroid or other immunosuppressant, or those with sight-threatening disease.</p> <p><u>Intervention:</u> Dose based on previous oncology dose ranging studies. Inadequate data on repeat dosing, concomitant steroid use, and duration of effects to understand long term benefit.</p> <p><u>Comparator:</u> Placebo; active comparator against current standard of care (i.e. corticosteroids) lacking</p> <p><u>Outcomes:</u> Proptosis appropriate surrogate, study not designed to study long term reduction of TED induced vision loss. Questions remain from FDA regarding appropriateness of CAS and validity of GO-QOL tools.</p> <p><u>Setting:</u> 13 sites in US and Europe</p>
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Abbreviations: AE = adverse events; ARR = absolute risk reduction; b/t = between; CAS = Clinical Activity score; CI = confidence interval; DB = double blind/masked; d/c = discontinued; DM = diabetes mellitus; dx = diagnosis; ex = except/exception; FT3 = free triiodothyronine; FT4 = free thyroxine ; GD = Graves' disease; GO-QOL = Graves' Orbitopathy Quality of Life Questionnaire; HbA1c = hemoglobin A1C; hx = history; ITT = intention to treat; IV = intravenous; LS = least squares; mITT = modified intention to treat; m = months; mm = millimeter; MMRM = Mixed Model Repeated Measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = Odds ratio; PC = placebo controlled; PCB = placebo; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; TEP = teprotumumab; tx = treatment; US = United States; wk = week; y = years.

Plus/minus values (\pm) are mean \pm SD

*Amended after study initiation^{22,25}

†Authors defined "clinical relevance" as a change of at least 8 points.^{1,22} A 6 point change is considered clinically relevant and the tool is considered valid by EUGOGO.²¹ The FDA had not received validation information and does not interpret GO-QOL scores in NDA application review.¹⁰

‡Results in table from study publication.^{2,26} Values differ in FDA review (PCB -0.5 mm vs TEP -2.8 mm; LSM -2.3 mm, 95% CI -2.8 mm to -1.8 mm).¹⁰

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TEPEZZA safely and effectively. See full prescribing information for TEPEZZA.

TEPEZZA (teprotumumab-trbw) for injection, for intravenous use
Initial U.S. Approval: 2020

-----INDICATIONS AND USAGE-----

TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease (1)

-----DOSAGE AND ADMINISTRATION-----

- Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (2.1)
- Administer TEPEZZA by intravenous infusion over 60 to 90 minutes (2.3)

-----DOSAGE FORMS AND STRENGTHS-----

For Injection: 500 mg lyophilized powder in a single-dose vial for reconstitution (3)

-----CONTRAINDICATIONS-----

None (4)

-----WARNINGS AND PRECAUTIONS-----

- Infusion reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)

- Exacerbation of Preexisting Inflammatory Bowel Disease (IBD) : Monitor patients with preexisting IBD for flare of disease; discontinue TEPEZZA if IBD worsens (5.2)
- Hyperglycemia: Monitor glucose levels in all patients; treat hyperglycemia with glycemic control medications (5.3)

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence greater than 5%) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

Females of Reproductive Potential: Appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2020

Teprotumumab

Goal(s):

- To ensure appropriate use of teprotumumab in patients with Thyroid Eye Disease (TED)

Length of Authorization:

- 8 total lifetime doses (approve for 9 months)

Requires PA:

- Teprotumumab

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the patient an adult (18 years or older)?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the medication being ordered by, or in consultation with, an ophthalmologist or specialized ophthalmologist (e.g. neuro-ophthalmologist or ocular facial plastic surgeon)?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Does the patient have active TED? <ul style="list-style-type: none"> • Defined as Clinical Activity Score (CAS) of 4 or higher on 7 point scale within past 3 months. 	Yes: Go to #5 CAS score: _____ Score date: _____	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria

<p>5. Does the patient have moderate, severe, or sight-threatening TED?</p> <ul style="list-style-type: none"> • Defined by the Graves' Orbitopathy Severity Assessment • Possible severity ratings are mild, moderate, severe, and sight-threatening. 	<p>Yes: Go to #6</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>6. Is the patient currently euthyroid (thyroid hormone levels no more than 50% above or below of normal range) within past 3 months?</p>	<p>Yes: Go to #7</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>7. Does the patient have <u>any</u> of the following:</p> <ul style="list-style-type: none"> • a contraindication or severe side effect* to corticosteroids <u>or</u> • failed to respond to 6 weeks of low-dose corticosteroid prophylaxis after radioactive iodine treatment <u>or</u> • failed to respond/relapsed after at least 3 weeks of high-dose (IV or oral) corticosteroids <p>*Note:</p> <ul style="list-style-type: none"> • Teprotumumab is associated with hyperglycemia which may necessitate diabetic medication changes and may not be an appropriate alternative when avoiding steroids in patients with uncontrolled diabetes mellitus. 	<p>Yes: Go to #8</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Approval Criteria

<p>8. Is the patient male <u>or</u> female without childbearing potential?</p> <p>Female without childbearing potential defined as:</p> <ul style="list-style-type: none"> • Onset of menopause >2 years before current date <u>or</u> • Non-therapy-induced amenorrhea >12 months before current date <u>or</u> • Surgically sterile (absence of ovaries and/or uterus, or tubal ligation) <u>or</u> • Not sexually active 	<p>Yes: Go to #11</p>	<p>No: Go to #9</p>
<p>9. Is there documentation of negative pregnancy test within past 4 weeks?</p>	<p>Yes: Go to #10</p> <p>Type of test (urine or serum): _____</p> <p>Date of test:_____</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>10. Has patient been counselled on risk of fetal harm AND agreed to use <u>at least</u> one reliable form of contraceptive for entire duration of drug therapy <u>and</u> for 180 days (6 months) after final dose?</p> <ul style="list-style-type: none"> • Reliable forms of birth control have less than 1% failure rate/year with consistent and correct use • Examples include: implants, injectables, combined oral/intravaginal/transdermal contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner • Hormonal methods should be started at least one full menstrual cycle prior to initiation of teprotumumab. 	<p>Yes: Go to #11</p> <p>Date of Counselling: _____</p> <p>Contraceptive method:_____</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Approval Criteria

11. Has the patient previously received any doses of teprotumumab?

Yes: Approve balance to allow 8 total lifetime doses[†]

(8 doses – previous # doses = current approval #)

Previous number of doses_____

No: Approve 8 doses[†]

[†] All approvals will be referred for and offered optional case management

*P&T/DUR Review: 12/20 (SF)
Implementation: 1/1/2021*