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Prior Authorization Criteria Update: Teprotumumab-trbw (Tepezza®)

Purpose of Update:
Evaluate the evidence for efficacy and safety of teprotumumab since the previous Pharmacy and Therapeutics (P & T) committee review in December 2020 and to align prior authorization criteria with an expansion of the Food and Drug Administration (FDA) approved indication.

Plain Language Summary:

- Thyroid eye disease, sometime also called Graves' Orbitopathy, is a disease that can result in sore, gritty, or red eyes, double vision, reduced sight, and blindness. Thyroid eye disease can range from mild, moderate, severe, or sight threatening. Thyroid eye disease is also either "active" where symptoms usually get worse, or "inactive", where symptoms stay stable but may still be severe.
- Teprotumumab is a medicine that has been approved to treat active thyroid eye disease for several years. In 2023, the Food and Drug Administration approved teprotumumab to also be used in inactive thyroid eye disease.
- When studied in patients with inactive thyroid eye disease, teprotumumab reduced eye bulging more than placebo (a look-alike that has no active medicine). Treating three patients with teprotumumab could reduce eye bulging by at least 2 mm for one patient. A change of 2 mm is likely enough to improve the quality of life for a person with thyroid eye disease.
- Mild muscle spasms occur more often in patients taking teprotumumab than placebo. High blood sugar and hearing impairment have also occurred in patients taking teprotumumab. Hearing impairment is sometimes permanent.
- Guidelines recommend using a medicine called glucocorticoids, or "steroids", first for most patients who have moderate to severe, active thyroid disease before teprotumumab.
- For people with fee-for-service Medicaid, the Oregon Health Plan will currently pay for teprotumumab for people with active thyroid eye disease. DURM recommends updating this policy to include patients with inactive thyroid eye disease.

Conclusions:

- Two clinical trials[1,2], one high quality guideline[3], one label expansion[4,5], and 2 Food and Drug Administration (FDA) safety labeling edits[6] have been published since teprotumumab was last reviewed.
- Teprotumumab was compared to placebo in a single, double-blind, randomized controlled trial (RCT) in patients with inactive thyroid eye disease (TED). Teprotumumab reduced proptosis more than placebo from baseline to week 24 (teprotumumab -2.41 mm vs. placebo -0.92; difference -1.48 mm; 95% confidence interval [CI] -2.28 to -0.69; P=0.0004, low quality evidence). Proptosis response (≥2 mm reduction from baseline) was achieved in 61.9% of teprotumumab patients compared to 25.0% of placebo patients (absolute risk reduction [ARR] 36.9%; 95% CI 5.4 to 59.2%; P=0.0134, number needed to treat [NNT] 3, low quality evidence).[1]

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- Muscle spasms occurred in 41.5% of teprotumumab patients versus 10% of placebo patients. Hearing impairment occurred in more teprotumumab patients (22%) compared to placebo (10%).[1] One teprotumumab patient experienced hearing loss and discontinued treatment.[1] Hyperglycemia occurred in 14.6% teprotumumab treated patients and 10% of placebo patients, however 1 of the 2 placebo categorized patients experienced diabetic ketoacidosis after receiving teprotumumab in error.[1]
- The FDA has strengthened the package labeling for hyperglycemia and added a new subsection for severe hearing loss, sometimes permanent, to warnings and precautions of the medication package insert.[6]
- A consensus statement American Thyroid Association (ATA) and European Thyroid Association (ETA) recommended intravenous glucocorticoids (IVGC) as first-line therapy for active, moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia.[3] Teprotumumab is a preferred therapy, if available, in patients with active moderate-to-severe TED with significant proptosis and/or diplopia.[3]
- Data on retreatment with teprotumumab in patients who have not had an adequate response after initial therapy, or have a disease flare after treatment, is insufficient.[2]

Recommendation:

- Update prior authorization (PA) criteria as amended in **Appendix 1**.

Background and Current Policy:

Teprotumumab was reviewed by the P & T committee in December 2020 for the treatment of active TED (also referred to as Graves' Orbitopathy [GO]) where it was designated as non-preferred with specific PA criteria on the Preferred Drug List (PDL) to ensure safe and appropriate use. Detailed background information related to the acute and chronic phases of this disease and various measurement scales are included in that document.[7]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted during the search period of 7/29/2020 to 1/16/24. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 6 systematic reviews[8-13] were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

The American Thyroid Association (ATA) and European Thyroid Association (ETA) jointly published a consensus statement on the Management of TED in 2022.[3] The consensus statement scope was to address clinical assessment and develop criteria for referral to specialty care and treatment, as well as to focus on medical and surgical treatment in nonpregnant adults (18 years and older) with TED. The primary audience for the guideline was endocrinologists. Two patient-led organizations were invited to review the draft and feedback was also received from the American Academy of Ophthalmology and the American Society of Ophthalmic Plastic and Reconstructive Surgery.[3]

Recommendations were presented as "Key Points" and therapies were prioritized as (1) preferable, (2) acceptable, or (3) may be considered. Preferred therapies are supported by evidence from 2 or more RCTs that have shown efficacy against standard of care or placebo with concordant results. Acceptable therapies were defined as at least 2 RCTS with discordant results where the discordance is likely the results of different inclusion criteria or based on a single RCT showing efficacy.[3] Therapies were categorized as "may be considered" when benefit is not clear, and are typically used in clinical practice when preferred and acceptable therapies are unavailable, contraindicated, or not tolerated.

Proptosis was discussed in the consensus statement recommendations as a disease manifestation of TED which might affect preference for one treatment modality over another. "Significant proptosis" is usually defined in the literature as ≥3 mm above the upper limit for race and sex. The authors felt patients with moderate-to severe TED and a degree of proptosis of <3 mm above the upper limit for race and sex could also be defined as "significant proptosis" if it sufficiently impacted daily life and would justify the risks of treatment, in addition to using the standard numeric threshold.[3]

Key points delineating place in therapy for teprotumumab relative to other pharmacotherapy or surgical options are included below.

- Key Point 6.1.1: A single course of selenium selenite 100 µg twice daily for 6 months may be considered for patients with mild, active TED, particularly in regions of selenium insufficiency.[3]
- Key Point 7.1.1.1: Intravenous glucocorticoid (IVGC) therapy is a preferred treatment for active moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia.[3]
- Key Point 7.1.1.2: Standard dosing with IVGC consists of IV methylprednisolone (IVMP) at cumulative doses of 4.5 g over ~3 months (0.5 g weekly × 6 weeks followed by 0.25 g weekly for an additional 6 weeks).[3]
- Key Point 7.1.1.3: Poor response to IVMP at 6 weeks should prompt consideration for treatment withdrawal and evaluation of other therapies. Clinicians should be alert for worsening diplopia or onset of dysthyroid optic neuropathy that have occurred even while on IVMP therapy.[3]
- Key Point 7.1.2.1: Rituximab and tocilizumab may be considered for TED inactivation in GC-resistant patients with active moderate-to-severe TED. Teprotumumab has not been evaluated in this setting.[3]
- Key Point 7.1.3.1: Teprotumumab is a preferred therapy, if available, in patients with active moderate-to-severe TED with significant proptosis and/or diplopia.[3]
- Key Point 7.1.4.1: Evidence from RCTs is limited and divergent but suggests efficacy of rituximab for inactivation of TED and prevention of relapses at >1 year, particularly in patients with TED of <9 months duration.[3]
- Key Point 7.1.4.2: Rituximab therapy is acceptable in patients with active moderate-to-severe TED and prominent soft tissue involvement.[3]
- Key Point 7.1.6.1: Tocilizumab is an acceptable treatment for TED inactivation in GC-resistant patients with active moderate-to-severe disease.[3]

- Key Point 8.1.1: Patients with dysthyroid optic neuropathy require urgent treatment with IVGC therapy, with close monitoring of response and early (after 2 weeks) consideration for decompression surgery if baseline visual function is not restored and maintained with medical therapy.[3]

Additionally, clinical comorbidities should be considered and may affect treatment preference. In patients with a chronic infection, teprotumumab is rated as a "favored choice" or "may be favored choice" along with radiotherapy (rated "may be favored choice"). In patients with liver disease, teprotumumab is a "favored choice" or "may be favored choice" along with radiotherapy or rituximab (both rated "may be favored choice").[3]

Additional Guidelines for Clinical Context:
The European Group on Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy were updated in 2021.[14] The methods relating to PubMed search strategies are not well described and several members of this *ad hoc* task force had significant conflicts of interest. This guideline will be presented for clinical context only.

Mild GO should be treated with local treatments and general measures to control risk factors and a 6-month selenium supplementation should be given to patients with mild and active GO of recent onset (moderate quality evidence).[14] If the impact on quality of life outweighs risks, then low-dose immunomodulatory therapy (in active GO) or rehabilitative surgery (in inactive GO) is proposed after to extensive counseling and shared decision making (low quality evidence).[14]

An intermediate dose of IVGC should be used in most cases of moderate-to-severe and active GO (high quality evidence), and high dose IVGC should be reserved for more severe cases (constant/inconstant diplopia, severe proptosis, severe soft-tissue pathology or involvement) (moderate quality evidence).[14] The cumulative dose of IVGC should not exceed 8.0 g each cycle, and patients with certain comorbidities including recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, uncontrolled hypertension, and uncontrolled diabetes mellitus should not receive IVGC (moderate quality evidence).[14] Teprotumumab is listed as a "very promising drug with strong reduction of exophthalmos, diplopia, and improvement of quality of life. Currently, [teprotumumab is a] second-line option as longer-term data, availability, affordability, costs, and need for subsequent rehabilitative surgery are pending" (moderate quality evidence).[14]

The first-line treatment recommendation for moderate to severe and active GO are IVMP in combination with mycophenolate sodium (or mofetil) based on moderate quality evidence.[14] In moderate-to-severe disease that is on the more severe end of the severity range and active GO, such as patients with constant/inconstant diplopia, severe inflammatory signs, and exophthalmos > 25 mm, high dose IVMP monotherapy is recommended as an additional first-line treatment (moderate quality evidence).[14]

Second-line treatments should be considered when response to primary treatment is poor and GO is still moderate-to-severe and active. Options include a second course of IVMP, oral prednisone/prednisolone combined with cyclosporine or azathioprine, orbital radiotherapy combined with oral or IVGC, teprotumumab, rituximab, or tocilizumab (moderate quality evidence).[14]

New FDA Approvals:
In April 2023 the Food and Drug Administration (FDA) expanded the approved indication for teprotumumab from treatment of thyroid eye disease (TED) to treatment of TED *regardless of activity or duration*.[4,5] Additional important safety edits to the package insert have been made since the initial approval (**Table 1**).

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[6]

Month / Year of Change	**Location of Change (Boxed Warning, Warnings, CI)**	**Addition or Change and Mitigation Principles** (updated underlined)
December 2022	Warning and Precautions	• Updates to "Hyperglycemia" subsection • Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre- existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA.
July 2023	Warnings and Precautions	• New "Hearing Impairment Including Hearing Loss" subsection • May cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

Randomized controlled trials:

Evidence previously reviewed by the Pharmacy and Therapeutics Committee for teprotumumab included patients with acute TED with a duration of ≤ 9 months and Clinical Activity Score (CAS) of ≥4.

New evidence in this update includes patients with chronic or low disease activity TED in a double-masked, placebo-controlled, randomized, phase 4 trial.[1] Adult patients who had TED with a duration of 2 to 10 years and a CAS of 0 or 1, indicative of inactive disease, were eligible to participate.[1] Additional inclusion and exclusion criteria are in **Table 3**. Patient were randomized 2:1 for 8 doses given once every 3 weeks of teprotumumab (n= 42) or placebo (n=20).[1] Mean age was 48.7 years (standard deviation [SD] 14.9 years).[1] Baseline characteristics were similar with a few exceptions. Fewer female patients were assigned to the teprotumumab group (76.2%) than placebo (90.0%), more Asian participants were assigned to teprotumumab (16.7%) than placebo (5.0%), and slightly more patients randomized to teprotumumab (33.3%) had diplopia (intermittent, inconstant, or constant) than placebo (20.0%).[1] Historical use of other therapeutic modalities for TED were not reported.[1] The primary endpoint of reduction in proptosis in study eye from baseline to week 24 was higher for teprotumumab than placebo (teprotumumab -2.41 mm vs. placebo -0.92 mm, difference -1.48 mm; 95% CI -2.28 to -0.69, p=0.0004).[1] Additionally, more patients receiving teprotumumab were proptosis responders (at least 2 mm improvement in proptosis from baseline) than placebo (teprotumumab 61.9% mm vs. placebo 25.0%, difference 36.9% mm; 95% CI 5.4 to 59.2%, P=0.0134, number needed to treat [NNT] 3).[1] Improvements in the Graves' Ophthalmopathy Quality of Life (GO-QOL) visual function subscale were statistically significant in favor of teprotumumab (LSM difference 6.31, 95% CI 0.57 to 12.06, p=0.0318), but not for the GO-QOL appearance related subscale (LSM difference 2.85, 95% CI -9.62 to 15.32, p=0.649).[1] A minimum change of 6 points on either subscale is generally considered to be meaningful.[15]

Adverse events of special interest (AESI) included infusion reactions, hyperglycemia, hearing impairment, new onset inflammatory bowel disease (IBD) and exacerbation of IBD. No patients developed new onset or exacerbation of IBD; other results are presented in **Table 3**.[1] Muscle spasms were the most frequently reported adverse event, generally of the lower extremities and all were mild.[1] The most common AEs are summarized in **Table 2**. Two patients discontinued due to serious adverse events related to conductive deafness in a teprotumumab patient with a congenital abnormality and diabetic ketoacidosis in a placebo

categorized patient who received teprotumumab in error for the first treatment dose and was reported to have had undiagnosed diabetes mellitus and uncontrolled glucose levels. Trial methods specify exclusion for Hemoglobin A1C of more than 8% at enrollment.[1] Nine patients receiving teprotumumab reported hearing impairment and 3 of 9 were reporting improvement or recovery at the time of data collection.[1]

Table 2. Common adverse events[1]

Adverse Event	**Teprotumumab**	**Placebo**
Muscle Spasm	41.5%	10%
Fatigue	22.0%	10.0%
Headache	17.1%	10.0%
Dry skin	12.2%	0%
Eye pain	12.2%	5%
Eye pruritus	7.3%	0%
Hemoglobin A1C increase	7.3%	0%
Hypertension	7.3%	0%

The OPTIC-X study is an open-label, single-arm, extension study of OPTIC (which evaluated patients with acute TED) and was published in 2021.[2] Given the open-label trial design and high risk of bias with lack of placebo group this study will not be reviewed extensively. However, minimal information is available regarding durability of response and retreatment with teprotumumab. Non-responders in the original study were eligible for re-treatment (teprotumumab group) or first treatment (placebo group) at the end of the OPTIC protocol.[2] Patients who initially had responded during OPTIC (proptosis reduction of at least 2 mm from baseline) who experienced a disease flare were also eligible for treatment/re-treatment.[2] Flare was defined as increase in proptosis of 2 mm or more in the study eye and/or increase in CAS score of at least 2 points with total of 4 points or more.[2] This trial was conducted during the COVID-19 pandemic, and patients who were not present for the 24-week assessment were not included in the 24-week analysis for categorical variables.[2] The number of visits missed due to COVID-19 was not reported. There was an active treatment period of 24 weeks in OPTIC-X, followed by at 24-week follow-up period.

In the OPTIC trial, 39 of 41 patients randomized to teprotumumab completed the treatment period, and 5 of those were non-responders.[2] During OPTIC-X, 2 of those 5 patients who began retreatment discontinued early (1 lack of efficacy, 1 intracerebral hemorrhage), 2 patients had a proptosis reduction of 2 mm or more from the OPTIC-X baseline (in addition to the 1-1.5 mm reductions from the OPTIC baseline to start of OPTIC-X), and 1 patient had a 0.5 mm proptosis reduction from the OPTIC-X baseline.[2]

Thirty-three of the 34 teprotumumab responders from OPTIC continued in OPTIC-X, plus one patient who did not complete the double-blind treatment period of OPTIC. A disease flare was experienced by 10/34 of those patients (29.4%), 7 of them by week 48.[2] One of the 10 patients was ineligible for retreatment due to dysthyroid optic neuropathy and the remaining 9 were retreated in OPTIC-X . One of those was excluded from week 24 summaries due to missing that appointment secondary to COVID-19.[2] Proptosis response was achieved in 5 of 8 patients who were retreated after flare and had a week 24 assessment.[2]

In patients receiving retreatment with teprotumumab, one serious adverse event (cerebral hemorrhage) was reported.[2] It is unclear if this was related to the study medication as the patient had other risk factors for hemorrhage. No other serious adverse events or drug discontinuations due to adverse events were

reported.[2] Muscle spasm (28.6%), arthralgia (14.3%), back pain (14.3%), alopecia (14.3%), dry skin (14.3%), nasal dryness (14.3%), hearing impairment (14.3%), diarrhea (7.1%), and potential infusion-related reaction (7.1%) were reported.[2] No patients reported hyperglycemia during retreatment.[2]

A total of 3 citations[16-18] were manually reviewed from the initial literature search and were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Table 3. 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. Douglas, et al.[1] DB, PC, RCT	1. Teprotumumab 10 mg/kg first infusion then 20 mg/kg every 3 wk x 7 infusions 2. Placebo every 3 weeks x 8 infusion 2:1 randomization	Demographics: - Mean age 48.7 y (SD 14.9) - Female 1. 76.2% 2. 90.0% - Ethnicity -White 54.8% -Black 24.2% -Asian 1. 16.7% 2. 5.0% - Mean time since dx: 5.1-5.4 y - Current tobacco use: 12.9% - Mean proptosis study eye: 24.0-24.6 mm - Patients with diplopia 1. 14 (33.3%) 2. 4 (20.0%) - Mean CAS study eye: 0.3-0.5 - Mean GO-QOL visual functioning subscore 1. 86.4 2. 81.4 - Mean GO-QOL appearance subscore 1. 46.4 2. 40.0 Key Inclusion Criteria: - Age ≥ 18 years - TED duration 2 to <10 y - Stable/inactive disease defined as: CAS ≤ 1 in both eyes for at least 1 year OR no proptosis	ITT: 1. 42 2. 20 Attrition: 1. 3 (7%)* 2. 1 (5%) (d/c AE) *1 randomized, with d/c before drug receipt, 2 lost to follow-up	Primary Endpoint: Change in proptosis in study eye from baseline to Week 24; LSM (SE) 1. -2.41 (0.23) mm 2. -0.92 (0.32) mm Difference -1.48 mm 95% CI -2.28 to -0.69 P=0.0004 Secondary Endpoint: Proptosis responders (≥ 2mm reduction from baseline in proptosis in study eye) 1. 26/42 (61.9%) 2. 5/20 (25.0%) Difference 36.9% 95% CI 5.4 to 59.2% P =0.0134 Change from baseline in GO-QOL Visual Function Subscale LSM (SE) 1. 8.73 (1.661) 2. 2.41 (2.329) Difference 6.31 95% CI 0.57 to 12.06 P=0.0318	NA ARR 36.9%/ NNT 3 NA	Any AE 1. 33/42 (80.5%) 2. 16/20 (80%) Muscle Spasms 1. 17 (41.5%) 2. 2 (10%) Serious AE 1. 1 (2.5%) - conductive deafness 2. 1 (5%) – DKA† D/c due to AE 1. 1 (2.5%) - hearing loss 2. 1 (5%) - infusion related AESI Hearing Impairment 1. 9 (22%) 2. 2 (10%) Hyperglycemia 1. 6 (14.6%) 2. 2 (10%)† Infusion-related reactions 1. 2 (4.9%) 2. 3 (15%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization 2:1 without stratification by contract research organization using electronic data capture system. Some imbalances in baseline characteristics, and it is unclear if these differences would impact results. Performance Bias: (Unclear) Patients, investigators, trial site personnel (except pharmacists compounding trial medication) and data assessors blinded until study end. Method not described. Certain side effects more common with active drug (i.e., Muscle spasms). At least one placebo patient received active drug in error. Detection Bias: (Low) Patients, investigators, trial site personnel (except pharmacists compounding trial medication) and data assessors blinded until study end. Method not described. Primary endpoint was an objective measurement. Attrition Bias: (Low) Overall attrition was low. Missing data not imputed unless methods for handling missing data are specified per the report. Patients missing week 24 data for categorical endpoints were considered non-responders. Reporting Bias: (Low) Major endpoints reported. Protocol not found. Other Bias: (Unclear) Study sponsor was drug manufacturer and had roll in designing, collecting data, and writing the final report. **Applicability**:

		progression, no diplopia progression, & no new inflammatory TED symptoms - ≥ 3 mm increase in proptosis from before dx of TED and/or proptosis ≥ 3mm above normal for race & sex -Euthyroid (mild excursions allowed) <u>Key Exclusion Criteria</u>: -h/o strabismus surgery or orbital decompression -↓ visual acuity due to optic neuropathy or visual field/color defect 2° to optic nerve involvement in ≤ 6 mo - Other tx: GC use within 3 wks, rituximab within 12 mo, tocilizumab with 6 mo, non-steroid immunosuppressive within 3 mo, any monoclonal antibody within 3 mo, any h/o teprotumumab. - Pregnancy - HbA1C > 8% - h/o IBD, UC, active Crohn's disease or remission < 3 months or bowel surgery in ≤ 6 months from screening		Change from baseline in GO-QOL Appearance Subscale LSM (SE) 1. 10.03 (3.592) 2. 7.19 (5.069) Difference 2.85 95% CI -9.62 to 15.32 P=0.649	NS	†DKA experienced by undiagnosed DM patient in placebo group who received teprotumumab in error		<u>Patient</u>: More female than male participants is reflective of the underlying disease. Relatively good inclusion of diverse racial demographics. Population comorbidity exclusions should be noted when selecting specific TED therapies. Historical treatment experience not reported. <u>Intervention</u>: Dosing appropriate based on past studies and FDA label. <u>Comparator</u>: Placebo appropriate to establish efficacy for non-acute use. However, comparison to other therapies would be useful. <u>Outcomes</u>: Similar outcomes in previous trials for this medication. Proptosis response of ≥ 2 mm is expected to be clinically meaningful as it can reduce diplopia and improve corneal lid coverage.[19] <u>Setting</u>: 11 US centers

<u>Abbreviations</u>: AE = adverse event; AESI = adverse events of special interest; ARR = absolute risk reduction; CAS = clinical activity score; CI = confidence interval; CV = cardiovascular event; DB = double blind; d/c = discontinue; DKA = diabetic ketoacidosis; DM = diabetes mellitus; dx = diagnosis; dx = diagnosis; FDA = Food and Drug Administration; GC = glucocorticoid; GO-QOL = Graves' Ophthalmopathy Quality of Life; HbA1C = hemoglobin A1C; h/o = history of; HR = hazard ratio; HTN = hypertension; IBD = irritable bowel disease; ITT = intention to treat; LSM = least squares mean; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; OR = orbital radiation; PC = placebo controlled; pt = patient; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TED = thyroid eye disease, tx = treatments; UC = ulcerative colitis; w/d = withdrew; wks = weeks; y = years.

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Appendix 1. Proposed Prior Authorization Criteria

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 (pharmacy and provider administered claims)

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 **moderate**, **severe**, or **sight-threatening** TED? • Defined by the Graves' Orbitopathy Severity Assessment. Possible severity ratings are mild, moderate, severe, and sight-threatening.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4.5. Does the patient have **active** TED? • Defined as Clinical Activity Score (CAS) of 4 or higher on 7 point scale within past 3 months.	**Yes:** Go to #6 CAS score:_____ Score date:_____	**No:** ~~Pass to RPh. Deny; medical appropriateness~~ Go to # 8
~~5.6. Is the patient currently euthyroid (thyroid hormone levels no more than 50% above or below of normal range) within past 3 months?~~	~~**Yes:** Go to #7~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
6. Does the patient have any of the following: • active viral hepatitis, chronic liver disease, or a significant chronic infection or • a contraindication or severe side effect* to intermediate or high dose* corticosteroids or • failed to respond to 6 weeks of low-dose corticosteroid prophylaxis after radioactive iodine treatment or • failed to respond/relapsed after at least 3 weeks of intermediate or high dose* (IV or oral) corticosteroids *Note: • 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. • Steroid regimens may vary. Example intermediate steroid regimen: 0.5 g/week for 6 weeks then 0.25 g/week for additional 6 weeks for cumulative dose 4.5 g IV methylprednisolone over ~ 3 months. Example high-dose steroid regimen: IV methylprednisolone 0.75 g/week for 6 weeks then 0.5 g/week for 6 weeks.	**Yes:** Go to #9	**No:** ~~Pass to RPh. Deny; medical appropriateness~~ Go to #7

Approval Criteria		
7. Dose the patient have documentation of diplopia or significant proptosis*? *Note: significant proptosis is defined as ≥ 3 mm above the upper limit for race and sex or < 3 mm but of sufficient severity to impact daily quality of life.	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~8. Does the patient have **inactive** TED?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
~~7.~~9. Is the patient of childbearing potential? Not considered of childbearing potential any of the following: • Onset of menopause >2 years before current date or • Non-therapy-induced amenorrhea >12 months before current date or • Surgically sterile (absence of ovaries and/or uterus, or tubal ligation) or • Not sexually active	**Yes:** Go to #10	**No:** Go to #12
~~8.~~10. Is there documentation of negative pregnancy test within past 4 weeks?	**Yes:** Go to #11 Type of test (urine or serum): _____ Date of test:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~9.~~11. ~~Has~~ Has the provider attested that the patient has been counselled on risk of fetal harm AND agreed to use at least one reliable form of contraceptive for entire duration of drug therapy and for 180 days (6 months) after final dose? • 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.	**Yes:** Go to #12 ~~Date of Counselling: _____~~ Contraceptive method:_____	**No:** Pass to RPh. Deny; medical appropriateness
12. Is there documentation that there has been a risk/benefit discussion with the patient related to risk of potentially permanent hearing impairment with teprotumumab AND documentation of a plan to assess/monitor hearing before, during, and after treatment?~~.~~	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
~~10.~~13. 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 : 4/24 (SF); 12/20 (SF)
Implementation: TBD; 1/1/2021