Subject: Tepezza (teprotumumab-trbw)	**Original Effective Date:** Q2 2020
Policy Number: MCP-365	**Revision Date(s):** Q3 2020
Review Date: Q4 2020	
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Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

This policy addresses Tepezza (teprotumumab-trbw) for the treatment of adults with thyroid eye disease when appropriate criteria are met.

The intent of this policy, Tepezza (teprotumumab-trbw), is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references and current peer-reviewed scientific literature. The information outlined in the Molina Clinical Policy includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Thyroid Eye Disease (TED) also referred to as Graves' Ophthalmopathy, Graves' Orbitopathy and Thyroid-Associated Ophthalmopathy (TAO). TED is an immune-mediated inflammatory disorder often associated with orbital inflammation, fibrosis, and fat expansion and produces expansion of the extraocular muscles and fat in the orbit. Characterized by enlargement of the extraocular muscles as well as an increase in the orbital fat volume. While symptoms are typically bilateral, they are often asymmetric. The most common presenting signs are orbital and periorbital edema, eyelid retraction, eyelid lag in downgaze, restrictive strabismus, compressive optic neuropathy, and exposure keratopathy with common symptoms of ocular irritation and dryness (Douglas RS, 2011). Many patients with TED present with a mild course of disease and can be treated symptomatically with supportive care and monitored for worsening. Moderate-to-severe TED, however, presents a therapeutic challenge since there have been no disease-modifying therapies available to reverse or reduce associated tissue damage and no FDA-approved agents indicated for the treatment TED (Hayes, 2020).

- The mainstay of treatment for patients with active, moderate-to-severe TED has been off-label glucocorticoids. Glucocorticoids have limited efficacy in TED with an estimated 50% of patients reporting inadequate symptom relief (Patel et al., 2019). In addition, glucocorticoids do not improve proptosis, a clinically significant symptom that can cause loss of sight (Douglas, 2019). Furthermore, lengthy use of steroid therapy has considerable side effects include increased risk of infection, worsening diabetes and/or hypertension, and weakening of bones.
- Patients with moderate-to-severe active disease may also receive immunosuppressive therapy aimed at reducing the inflammation. However, oral and intravenous steroids do not reverse the underlying pathophysiology and they may temporarily mask the symptoms of the disease without considerable effect on the disease progression including proptosis. Steroid sparing agents and human monoclonal antibodies approved for other inflammatory indications have been used in TED, but these agents have not demonstrated disease-modifying efficacy.
- Orbital radiotherapy or orbital decompression surgery may be required to treat patients whose vision is threatened.
- In the absence of effective pharmacotherapies, the only option left for patients is eventual surgery once the inflammatory process subsides. Pharmacotherapies targeting underlying pathogenic mechanisms for patients with active, moderate-to-severe TED had not been FDA approved prior to Tepezza.
- Tepezza provides an alternative nonsurgical treatment option that could potentially spare patients from multiple invasive surgeries

Tepezza (teprotumumab-trbw)

The first FDA-approved therapy specifically indicated for TED

- A fully human monoclonal antibody of the insulin-like growth factor type-1 receptor. The mechanism of action in patients with TED has not been fully characterized. Teprotumumab binds to insulin-like growth factor-1 receptor inhibitor and blocks its activation and signaling.
- FDA approval is supported by results from two studies consisting of a total of 170 patients: Phase 2 clinical study (Smith et. al., 2017) and Phase 3 confirmatory trial, OPTIC (Douglas et al., 2020).
    - Both trials enrolled adults with active moderate-to-severe TED and focused on evaluating the efficacy of teprotumumab in reducing proptosis and alleviating inflammatory symptoms. The OPTIC 24-week treatment period evaluated patients who received Tepezza or placebo once every three weeks for a total of eight infusions.
    - Results of the pivotal OPTIC trial demonstrated that Tepezza dramatically improved proptosis and reduced ocular symptoms of inflammation compared with placebo. Follow-up in this publication was limited to 24 weeks.

- 71 patients (83%) patients who received teprotumumab in study 1 and study 2, respectively, had a reduction in proptosis of greater than 2 mm, compared with 20% and 10% of patients who received placebo.
    - The OPTIC study found that significantly more patients treated with teprotumumab (83%) had a meaningful improvement in proptosis (≥ 2 mm) as compared with placebo patients (9.5%) ($p<0.001$) without deterioration in the fellow eye at week 24.
- Secondary end points were also reached in OPTIC. At week 24, 68% of patients treated with teprotumumab had a change from baseline of at least one grade in diplopia versus 29% of those receiving placebo. In an analysis of both trials, 53% of patients treated with teprotumumab had complete resolution of diplopia versus 25% of those receiving placebo.
- **Both trials were limited to 24 weeks. Further published evidence with larger sample sizes and longer-term follow-up to characterize the long-term benefit of Tepezza for the treatment of TED**: **OPTIC Phase 3 confirmatory clinical trial and the OPTIC-X open-label extension**

The OPTIC Phase 3 confirmatory clinical trial and the OPTIC-X open-label extension clinical trial to evaluate the long-term safety and efficacy of TEPEZZA in TED.

- The OPTIC Phase 3 confirmatory clinical trial included a 24-week treatment period and a 48-week off-treatment follow-up period.
    - Patients with TED were treated with Tepezza or placebo once every 3 weeks for a total of 8 infusions over 24-weeks and a 48th-week off-treatment follow-up period, without receiving any treatment for TED.
    - In the OPTIC 48-week off-treatment follow-up period, data indicates that 56% of participants (19/34; 56%) who received Tepezza and were proptosis responders at week 24 in the OPTIC trial maintained their proptosis response at week 72 without receiving additional thyroid eye disease treatment.
    - Similar durability from Week 24 to Week 72 was demonstrated for other endpoints in the OPTIC 48-week off-treatment follow-up period, including diplopia and CAS
- OPTIC-X, an open-label extension clinical trial, evaluated the safety and efficacy of teprotumumab in OPTIC participants who were either proptosis non-responders at week 24 or were proptosis responders at week 24 but relapsed during the 48-week off-treatment follow-up period.
    - In OPTIC-X, the majority of patients (89%) who received placebo during the OPTIC trial and then received teprotumumab (and therefore had a longer disease duration), similarly achieved the OPTIC primary endpoint of a 2 mm or more reduction in proptosis at week 24, with an average reduction of –3.5 mm.
    - Data from OPTIC-X provide evidence supporting the potential for Tepezza to meaningfully reduce proptosis in patients who have had TED for a longer period than what was originally studied in the Phase 2 and Phase 3 clinical trials.
- There were no new safety concerns in OPTIC-X or the OPTIC 48-week off-treatment follow-up period, including in patients who received additional Tepezza treatment.

FDA INDICATIONS

Thyroid eye disease Treatment of thyroid eye disease

Available as: 500 mg lyophilized powder in a single-dose vial for reconstitution
Approved by the FDA: January 21, 2020

- *Priority Review, Fast Track, Breakthrough Therapy, and Orphan Drug Designation.*

CLASSIFICATION: Monoclonal Antibody; Insulin-Like Growth Factor-1 Receptor (IGF-1R) Antagonist

Tepezza (teprotumumab-trbw) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified specialist in ophthalmology, endocrinology, oculoplastic surgery or neuro-ophthalmology. Submit consultation notes if applicable.

2. Diagnosis/Indication [ALL]

Documentation of ALL the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis.

- ❒ Diagnosis of Graves' disease associated with active thyroid eye disease (*TED)
  **Also referred to as Graves' Ophthalmopathy, Graves' Orbitopathy and Thyroid-Associated Ophthalmopathy (TAO)*

AND

- ❒ Baseline clinical activity score (CAS) of at least 4 (on the 7-item scale) in the *most severely affected eye*[OPTIC]
  - Refer to Appendix 2: Clinical Activity Score

AND

- ❒ Moderate-to-severe active phase TED that is non-sight threatening but has a significant impact on daily living defined as ONE or more of the following: [ONE]
  - ❍ Lid retraction greater than or equal to 2 mm
  - ❍ Moderate or severe soft tissue involvement
  - ❍ Exophthalmos greater than or equal to 3 mm above normal for race and gender
  - ❍ Inconstant or constant diplopia

AND

- ❒ Member has not had a decrease in best corrected visual acuity (BVCA) due to optic neuropathy within the previous six months (i.e., decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement)

AND

- ❒ For members new to Molina Healthcare: Prescriber attest that member has not received ≥ 8 Tepezza infusions (including the initial 10 mg/kg first infusion)

AND

- ❒ Documentation of ONE of the following: [ONE]
  - ❍ Member's thyroid level has been normalized prior to initiation of treatment, OR
  - ❍ Member is euthyroid or mildly hypo/hyper-thyroid with a free thyroxine (FT4) and free triiodothyronine (FT3) levels <50% above or below the normal limits

Informational note: In the Phase 3 confirmatory trial, participants were required to be euthyroid, although mild hypothyroidism or hyperthyroidism was allowed at screening (OPTIC). In the Phase 2 trial, enrollment criteria required euthyroid status; all patients had well-managed thyroid disease.

3. Age/Gender/Other restrictions [ALL]

- ❑ Member is 18 years of age
  - *Safety and effectiveness have not been established in pediatric patients.*

- ❑ Women of child-bearing potential: [ALL]
  - ❍ Negative serum pregnancy test within the past 30 days
    AND
  - ❍ Agrees to use effective contraception prior to initiation, during treatment, and for 6 months after the last dose

- ❑ Member does not have ANY of the following exclusions: [ANY]
  - ❑ Previous orbital irradiation or surgery for TED, or
  - ❑ Require surgical ophthalmological intervention, or
  - ❑ Biopsy-proven or clinically suspected inflammatory bowel disease (IBD), or
  - ❑ Poorly controlled diabetes
    - *Patients with pre-existing diabetes should be under appropriate glycemic control before receiving teprotumumab*

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Failure of a 12-week trial of a *systemic corticosteroid (up to maximally indicated doses), unless contraindicated or clinically significant adverse effects are experienced

  ** Systemic corticosteroids (not an all-inclusive list; may require PA):*
  - *Prednisone: 30 mg/day PO; Dose Limit/max dose: 30 mg/day*
  - *Methylprednisolone: 500 mg IV once weekly for weeks 1 to 6, then 250 mg IV once weekly for weeks 7-12. Dose Limit/max dose: 500 mg/week*

  MOLINA REVIEWER: Review profile for systemic corticosteroid claim and enter an authorization if applicable. Notify Prescriber if an authorization is entered.

  Informational Note: Glucocorticoids remain the mainstay of immunomodulatory therapy for moderate-to-severe Graves' orbitopathy (Davies TF, 2020). Although worsening orbitopathy may respond favorably and rapidly to oral prednisone therapy via its anti-inflammatory and immunosuppressive actions, IV glucocorticoid pulse therapy has become widely used for more severe orbitopathy and has the advantage of fewer side effects than high oral doses of prednisone. However, very high IV doses (cumulative doses greater than 8 g) have been seen to induce liver failure and must be avoided (UpToDate 2020).

5. ***Contraindications/Exclusions/Discontinuations to Tepezza (teprotumumab-trbw) therapy**
   **There are no contraindications listed in the manufacturer's labeling*
   Authorization will not be granted if ANY of the following conditions apply [ANY]
   - ❒ Non-FDA approved indications
   - ❒ Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to mAbs
   - ❒ Pregnancy
     - *Teprotumumab is a humanized monoclonal antibody (IgG1). Placental transfer of human IgG is dependent upon the IgG subclass, maternal serum concentrations, birth weight, and gestational age, generally increasing as pregnancy progresses. Based on the mechanism of action, and data from animal reproduction studies, in utero exposure to teprotumumab may cause fetal harm.*

   Exclusions
   - ❑ Previous orbital irradiation or surgery for TED
   - ❑ Require surgical ophthalmological intervention
   - ❑ Biopsy-proven or clinically suspected inflammatory bowel disease (IBD)

6. **Labs/Reports/Documentation required [ALL]**
   All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP are included.
   - ❑ Member's current weight (to authorize the appropriate amount of drug per the labeling)

   NOTE: *Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.*

REAUTHORIZATION /CONTINUATION OF THERAPY

Retreatment will not be authorized due to insufficient evidence of therapeutic value since clinical benefit beyond 24 weeks has not been established.

There is no published literature available at this time to support the use of Tepezza (teprotumumab-trbw) in patients who have already received a 24-week treatment (up to a total of 8 infusions over a 24-week period).
The OPTIC-X trial, which is currently ongoing, is designed to evaluate whether certain patients may benefit from retreatment or extended treatment, greater than 6 months, with Tepezza. OPTIC-X is a 48-week, open-label extension study in which patients who participated in the OPTIC Phase 3 clinical trial may receive up to 8 additional infusions of Tepezza. The primary endpoint is proptosis responder rate (the percentage of participants with ≥2 mm reduction in proptosis in the study eye) without deterioration (≥2 mm increase) of proptosis in the fellow eye. (NCT03461211)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosage [ALL]**
   Thyroid Eye Disease
   - ❑ Initial: 10 mg/kg as a single dose
   - ❑ Maintenance: 20 mg/kg IV infusion every 3 weeks for 7 additional infusions (8 infusions total including initial dosage)

2. **Authorization Limit [ALL]**
   - ❑ Quantity limit: [ALL]
     - ❍ Tepezza 500 mg single-dose vial for injection: 3 vials for initial dose followed by 5 vials for each of 7 additional doses
       AND
     - ❍ Dose does not exceed a single 10 mg/kg dose followed by seven 20 mg/kg infusions given every 3 weeks
   - ❒ Duration of authorization: **6 months** (up to a total of 8 infusions over a 24-week period)
   - ❒ Continuation of treatment: Will not be authorized beyond 6 months (and max total of 8 infusions)

3. **Route of Administration [ALL]**
   - ❑ Intravenous infusion; not to be administered as an intravenous push or bolus and not to be infused concomitantly with other agents.
   - ❑ May be authorized in a **physician office setting or an infusion center** only. Routine administration in a hospital or outpatient setting will not be authorized
   - ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11
   - ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

This policy addresses Tepezza (teprotumumab-trbw) for the treatment of adults with thyroid eye disease when appropriate criteria are met.

All other uses of Tepezza (teprotumumab-trbw) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❒ Retreatment will not be authorized beyond 6 months (up to a total of 8 infusions over a 24-week period) due to insufficient evidence of therapeutic value since clinical benefit beyond 24 weeks has not been established.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

Tepezza (teprotumumab-trbw) was granted FDA approval for the treatment of thyroid eye disease based on results from two 24-week trials, a Phase 2 clinical study and a Phase 3 confirmatory trial (OPTIC), comparing teprotumumab with placebo in 171 patients with active, moderate-to-severe Graves' orbitopathy. In both trials, a greater proportion of patients in the teprotumumab group had a reduction in clinical activity score and degree of proptosis. There are no controlled head-to-head trials with glucocorticoids, the standard therapy for moderate-to-severe orbitopathy; however, Tepezza, a disease-modifying treatment, has been shown to have greater effects on proptosis and diplopia than experience with glucocorticoids. Additionally, longer-term follow-up is being studied in ongoing open-label extension to determine the long-term benefit of Tepezza for the treatment of TED. Efficacy in patients who relapsed after initially responding to Tepezza is currently being evaluated in the OPTIC X trial.

Phase 3 OPTIC

Treatment of Graves' Orbitopathy [Thyroid Eye Disease] to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study) (Douglas et al., 2020)

A randomized double-masked placebo-controlled phase III multicenter trial evaluating Tepezza in adult participants with Graves' disease, who had active, moderate-to-severe thyroid eye disease, had ocular symptoms that began within 9 months before the baseline assessment, and had a *Clinical Activity Score (CAS) of at least 4 in the more proptotic (study) eye. Participants were randomized to receive intravenous infusions of either Tepezza (n=41) (10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions) or placebo (n=42) once every 3 weeks for 21 weeks for a total of 8 infusions; the last trial visit of the treatment period was at 24 weeks.

*The Clinical Activity Score is based on 7 components: spontaneous retrobulbar pain, pain on attempted eye movements, conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica, and swelling of the eyelids. Each component is scored as present or absent (score of 1 or 0, respectively), and the Clinical Activity Score is given as the sum of the scores (range, 0 to 7, with higher scores indicating greater level of inflammation). Participants were required to be euthyroid, although mild hypothyroidism or hyperthyroidism was allowed at screening.

The primary outcome was a proptosis response (defined as a reduction in proptosis of ≥ 2 mm from baseline in the study eye without a corresponding increase of ≥ 2 mm in the fellow eye) at week 24. At week 24, the percentage of patients with a proptosis response was higher with Tepezza than with placebo (83% [34 patients] vs. 10% [4 patients], P<0.001).

Key secondary outcomes were a Clinical Activity Score of 0 or 1 at week 24, the mean change in proptosis across trial visits, a diplopia response at week 24, and the mean change in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire across trial visits. Outcomes were also evaluated in the contralateral eye. All secondary outcomes were significantly better in patients treated with Tepezza compared with placebo, including overall response (78% versus 7%), Clinical Activity Score of 0 or 1 (59% versus 21%), mean change in proptosis (−2.82 mm versus −0.54 mm), diplopia response (68% versus 29%), and the mean change in GO-QOL overall score (13.79 points vs. 4.43 points) (P≤0.001 for all comparisons).

Most adverse events were mild or moderate in severity; 2 serious events occurred in the Tepezza group, of which 1 (an infusion reaction) led to treatment discontinuation.

Phase II RCT (Smith et. al., 2017)

This double-blind trial randomized 88 adults in a 1:1 ratio to receive intravenous infusions of either Tepezza or placebo once every 3 weeks for 24 weeks (total of 8 infusions). Patients were stratified according to smoking status. All patients had active moderate-to-severe thyroid eye disease (TED), defined as a Clinical Activity Score (CAS) ≥ 4 in the more severely affected eye (study eye), and all were diagnosed ≤ 9 months after onset of TED symptoms. Enrollment criteria required euthyroid status; all patients had well-managed thyroid disease. The trial excluded patients with optic neuropathy, severe ocular surface erosion, and those who improved in CAS score ≥ 2 points between screening and baseline visit.

The primary outcome was a composite endpoint defined as a reduction in CAS of ≥ 2 points and a reduction in proptosis of ≥ 2 mm, as measured by Hertel exophthalmometer, in the study eye, in the absence of a corresponding amount of worsening in the non-study eye. This was assessed after 24 weeks of treatment in an intention-to-treat population of patients who received at least 1 infusion of Tepezza (n=42) or placebo (n=45.)

Secondary endpoints included CAS and proptosis severity measured separately as continuous variables over time, Graves' ophthalmopathy-specific quality-of-life (GO-QOL) score, and subjective diplopia assessment.

Despite stratification by smoking status, there were more smokers in the placebo group (n=18) than in the Tepezza group (n=11). Investigators used analytic methods when calculating P values to adjust for this imbalance. A statistically greater proportion of participants in the Tepezza group met the primary composite endpoint compared with placebo (69% versus 20%, respectively; P<0.001). At weeks 6, 12, 18, and 24, the reduction from baseline in proptosis and CAS statistically favored Tepezza over placebo (secondary outcomes). Of note, a reduction in proptosis of ≥ 4 mm was observed at week 24 in 40% of patients treated with Tepezza, while no patient in the placebo group achieved this outcome. Quality-of-life measures also statistically favored Tepezza over placebo, with the exception of the GO-QOL appearance subscale which did not statistically differ between the 2 groups.

Adverse events that occurred in > 5% of patients treated with Tepezza included nausea (19%), muscle spasms (19%), diarrhea (14%), hyperglycemia (12%), alopecia, dry skin, dysgeusia, headache, paresthesia, hearing impairment, and weight loss (7% for each event). A 48-week follow-up phase of this trial is ongoing to assess durability of treatment response.

Douglas (2019) reported that the proptosis outcome (≥ 2 mm reduction) was met in 71.4% of the Tepezza-treated patients as compared with 20% of the placebo-treated patients (P<0.001). The proptosis benefit was observed early in the trial (study week 6), and all individual patients demonstrated some benefit at week 24.

Confirmatory Trials

The OPTIC Phase 3 confirmatory clinical trial and the OPTIC-X open-label extension clinical trial to evaluate the long-term safety and efficacy of TEPEZZA in TED.

OPTIC 48-Week Follow-Up Period OPTIC (Treatment of Graves' Orbitopathy [Thyroid Eye Disease] to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo- Controlled, Clinical Study)

Phase 3 confirmatory clinical trial (a multicenter, randomized, double-blind, placebo-controlled trial) included a 24-week treatment period and a 48-week off-treatment follow-up period. At the end of the 24-week treatment period, patients who were proptosis responders entered into the 48-week off-treatment follow-up period, without receiving additional TED treatment, including TEPEZZA. Clinic visits were scheduled for Weeks 28, 36, 48, 60, and 72 (Months 7, 9, 12, 15, and 18). Sustained proptosis response in the OPTIC 48-week off-treatment follow-up period was defined as a 2 mm or more proptosis improvement from OPTIC baseline at Week 24, a 2 mm or more proptosis improvement from OPTIC baseline at Week 72 and no additional TED treatment, including TEPEZZA.

OPTIC-X (Treatment of Graves' Orbitopathy [Thyroid Eye Disease] to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study); (NCT03461211)

OPTIC-X was designed to evaluate whether certain patients may benefit from retreatment or longer treatment (more than 6 months) with TEPEZZA. OPTIC-X was a 48-week, open-label extension trial in which patients who participated in the OPTIC Phase 3 clinical trial received eight additional infusions of TEPEZZA (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining seven infusions). OPTIC-X evaluated the safety and efficacy of TEPEZZA in TED patients who were enrolled in OPTIC and were either proptosis *non-responders at Week 24 of OPTIC, or were proptosis responders at Week 24 but †relapsed during the 48-week off-treatment follow-up period.

*Non-responders were defined as patients who did not achieve at least a 2 mm proptosis improvement from baseline at Week 24 of OPTIC.

†Relapse was defined as patients who lost at least 2 mm of their Week 24 proptosis improvement during the 48-week off-treatment follow-up period (even if their proptosis was still substantially better than at baseline of OPTIC) or who had a substantial increase in the number of inflammatory signs or symptoms without worsening proptosis. Patients could qualify as relapsing at any point during the 48-week off-treatment follow-up period of OPTIC.

The primary endpoint was proptosis responder rate, which is defined as the percentage of participants with a 2 mm or more proptosis reduction since baseline of OPTIC-X in the study eye without deterioration of proptosis in the fellow eye (2 mm or more increase) at Week 24. **The estimated study completion date is March 2022.**

Top-line Data from the Phase 3 OPTIC and OPTIC-X trials in TED (July 31, 2020; Horizon Therapeutics)

- In the OPTIC 48-week off-treatment follow-up period, the majority of TEPEZZA patients who were proptosis responders at Week 24 in OPTIC maintained their proptosis response at Week 72 (19/34; 56 percent) without receiving additional TED treatment. Of the 15 patients who did not qualify as maintaining a proptosis response, eight patients were at least 2 mm better than baseline at the time of their last assessment in the OPTIC 48-week off-treatment follow-up period. The 15 patients include four who prematurely discontinued the study, two who had worsened slightly but not enough to qualify as relapsed for OPTIC-X and nine who met the OPTIC-X criteria for relapse prior to Week 72 of the off-treatment follow-up period (eight of whom entered OPTIC-X for retreatment and one who did not enroll in OPTIC-X).
- Similar durability from Week 24 to Week 72 was demonstrated for other endpoints in the OPTIC 48-week off-treatment follow-up period, including diplopia and CAS.
- 89% of patients (33/37) who received placebo during the OPTIC trial and then entered OPTIC-X and received TEPEZZA achieved the primary endpoint of a 2 mm or more reduction in proptosis at Week 24 (average reduction of -3.5 mm). This is consistent with results from the OPTIC trial, where 83 percent of TEPEZZA patients (n=41) had a proptosis reduction of 2 mm or more at Week 24 (average reduction of -3.3 mm).
- The results for other OPTIC-X endpoints, including diplopia and Clinical Activity Score (CAS), are similar to what was observed in OPTIC.
- These patients who received placebo in OPTIC and their first course of TEPEZZA in OPTIC-X had a TED diagnosis for an average of one year and as long as 16 months, compared with an average of six months in the OPTIC trial.
- For relapsed patients who were retreated with an additional course of TEPEZZA, more than 60% had a 2 mm or more proptosis improvement from OPTIC-X baseline at Week 24.
- Only five patients had not achieved a proptosis response after completing a full course of TEPEZZA in OPTIC. Of these, two achieved a 2 mm or more proptosis reduction in OPTIC-X after an additional course of TEPEZZA.
- There were no new safety concerns in OPTIC-X or the OPTIC 48-week off-treatment follow-up period, including in patients who received additional TEPEZZA treatment.

PRACTICE GUIDELINES AND POSITION STATEMENTS

At the time of this writing, no guidelines were identified that addressed the use of Tepezza to treat TED. Furthermore, there have been no U.S. guidelines published within the past 10 years identified that addressed the treatment of TED.

European Thyroid Association/European Group on Graves' Orbitopathy
The Guidelines for the Management of Graves' Orbitopathy addressing the treatment of TED was updated in 2016. The guidelines recommended high-dose systemic glucocorticoids for first-line treatment for moderate-to-severe and active TED with off-label rituximab listed as an option among second-line recommended therapies (EUGOGO, 2016).

DEFINITIONS

NA

APPENDIX

APPENDIX 1: Thyroid Eye Disease (TED)

Thyroid Eye Disease (TED) also referred to as Graves' Ophthalmopathy, Graves' Orbitopathy and Thyroid-Associated Ophthalmopathy (TAO)

- An immune-mediated inflammatory disorder often associated with orbital inflammation, fibrosis, and fat expansion and produces expansion of the extraocular muscles and fat in the orbit. Characterized by enlargement of the extraocular muscles as well as an increase in the orbital fat volume. While symptoms are typically bilateral, they are often asymmetric. The most common presenting signs are orbital and periorbital edema, eyelid retraction, eyelid lag in downgaze, restrictive strabismus, compressive optic neuropathy, and exposure keratopathy with common symptoms of ocular irritation and dryness (Douglas RS, 2011).
- Most commonly assocY7iated with Graves' hyperthyroidism but can also occur in association with other thyroid states, hypothyroid and euthyroid states. Approximately 40% of individuals with Graves' disease develop TED; smokers are particularly at risk for developing this disorder (Patel et al., 2019). The condition is seen in individuals with no other evidence of thyroid dysfunction, and occasionally in patients who have Hashimoto's Disease. However, most thyroid patients will not develop thyroid eye disease, and if so, only mildly so.
- The disease course of TED does not always coincide with thyroid activity or the treatment of underlying thyroid dysfunction, therefore the treatment of thyroid dysfunction does not necessarily affect course of Grave's ophthalmopathy (American Academy of Ophthalmology, 2019). The exact underlying etiology of TED is not yet completely understood, however, the presumed mechanism is related to autoimmune activation of orbital fibroblasts by Graves' disease-related autoantibodies (Mohyi and Smith, 2018).
- The demographics of thyroid-associated orbitopathy reflects that of patients with thyroid disease and is, therefore, more frequently seen in women. Risk factors for TED include age, gender, ethnicity, and family history. A positive family history of TED is also noted in a large population of TED patients.
    - The median age of diagnosis is 43 years for all patients, with a range from 8-88 years.
    - Patients diagnosed over the age of 50 years have a worse prognosis overall.
- Many patients with TED present with a mild course of disease and can be treated symptomatically with supportive care and monitored for worsening. Moderate-to-severe TED, however, presents a therapeutic challenge since there have been no disease-modifying therapies available to reverse or reduce associated tissue damage and no FDA-approved agents indicated for the treatment TED (Hayes, 2020).

- The mainstay of treatment for patients with active, moderate-to-severe TED has been off-label glucocorticoids. Glucocorticoids have limited efficacy in TED with an estimated 50% of patients reporting inadequate symptom relief (Patel et al., 2019). In addition, glucocorticoids do not improve proptosis, a clinically significant symptom that can cause loss of sight (Douglas, 2019). Furthermore, lengthy use of steroid therapy has considerable side effects include increased risk of infection, worsening diabetes and/or hypertension, and weakening of bones.
- Patients with moderate-to-severe active disease may also receive immunosuppressive therapy aimed at reducing the inflammation. However, oral and intravenous steroids do not reverse the underlying pathophysiology and they may temporarily mask the symptoms of the disease without considerable effect on the disease progression including proptosis. Steroid sparing agents and human monoclonal antibodies approved for other inflammatory indications have been used in TED, but these agents have not demonstrated disease-modifying efficacy.
- Orbital radiotherapy or orbital decompression surgery may be required to treat patients whose vision is threatened.
- In the absence of effective pharmacotherapies, the only option left for patients is eventual surgery once the inflammatory process subsides. Pharmacotherapies targeting underlying pathogenic mechanisms for patients with active, moderate-to-severe TED had not been FDA approved prior to Tepezza.
- Tepezza provides an alternative nonsurgical treatment option that could potentially spare patients from multiple invasive surgeries

APPENDIX 2: Clinical Activity Score (CAS)

Disease activity can be assessed using the clinical assessment score (CAS). This set of clinical criteria was initially described in 1989 *(Mourits et al. 1989)* and has been widely used in assessing patients with TED and in planning their treatment. The criteria include seven clinical parameters of inflammation easily determined in the clinic. Furthermore, they include changes in three functional parameters over a period of 1–2 months.

For each criterion met by the patient, one point is assigned, with a total CAS of 10. Patients with a low score (<3) respond poorly to immunosuppressive therapy, indicating that they have passed the disease stage of active inflammation (Mourits et al. 1989). Other studies have confirmed the clinical value of the CAS in determining disease activity and the likelihood of a response to immunosuppressive therapy. One study found that a CAS of 4 or more has a positive predictive value for a treatment response with corticosteroids of 80% (Mourits et al. 1997)

Determining the Clinical Activity Score (CAS)
At the initial visit, patients are given a CAS score of 1-7 (one point for each of the following signs or symptoms) • Spontaneous pain in or around the eye in the past 4 weeks (pain without eye movement) • Eye pain associated with eye movement in the past 4 weeks • Swelling of the eyelids • Redness of eyelids • Conjunctival injection (redness of the actual eyeball) • Chemosis (swelling of the eyeball) • Swelling of the caruncle (the red prominence at the inner corner of the eye) At subsequent follow-up visits, the 3 following criteria are added for a potential CAS score of 10 • Increase in proptosis/exophthalmos (bulging of the eye out of the eye socket) of the eye (by at least 2mm) • Decrease in motility of an eye in one direction (by at least 5º) • Decrease in vision (by at least 1 line on the Snellen chart)

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CPT	Description

HCPCS	Description
J3490, J3590	Unclassified drugs

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Policy History	Approval
Policy Developed Peer Review: AMR Peer Review Network. 3/13/2020. Practicing Physician. Board certified in Ophthalmology (KY)	P&T Q2 2020
Policy Revision 1) Revised step therapy criterion from 4-week to 12-week trial: Failure of a 12-week trial of a *systemic corticosteroid (up to maximally indicated doses), unless contraindicated or clinically significant adverse effects are experienced; and 2) Added criterion: For members new to Molina Healthcare: Prescriber attest that member has not received ≥ 8 Tepezza infusions (including the initial 10 mg/kg first infusion); and 3) Deleted 'Exclusion' criterion: Receiving or have received a total steroid dose, oral and intravenous, of greater than or equal to 1 gram of methylprednisolone for the treatment of TED	P&T Q3 2020
Annual Review Updated policy with the confirmatory trial top-line data from the Phase 3 OPTIC and OPTIC-X trials in TED released in July 31, 2020 by manufacturer (Horizon Therapeutics). Other policy content and coverage criteria were not changed based on this revision.	P&T Q4 2020

**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Policy Revisions.' Annual Reviews without notable changes to coverage criteria or position may not require Peer Review. Policy Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer.*