Thyroid Eye Disease Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
11-01-2024

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Tepezza® (teprotumumab-trbw) Injection powder	Treatment of thyroid eye disease regardless of thyroid eye disease activity or duration		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Thyroid Eye Disease	Thyroid eye disease (TED), also known as Graves' orbitopathy (GO), is an autoimmune disease that typically develops in patients with overactive thyroids. The American Thyroid Association (ATA) notes that 90% of patients that develop thyroid eye disease have a current diagnosis or history of Graves' disease, and roughly 40% of patients with Graves' disease go on to develop TED symptoms, which are generally mild and treatable.(3,7) Symptoms can occur any time, but usually begin within 1 year of initial diagnosis of Graves' disease. Symptoms include feeling of irritation or grittiness in the eyes, redness or inflammation of the conjunctiva, excessive tearing or dry eyes, swelling of the eyelids, sensitivity to light, forward displacement or bulging of the eyes (also known as proptosis), and double vision (also known as diplopia). Incomplete closure of the eyelid, compression of the optic nerve, and rarely loss of vision can occur in more advanced eye disease.(2) Thyroid eye disease is believed to develop from the activation of orbital fibroblasts by autoantibodies that target thyrotropin receptors (TSHR) or insulin-like growth factor-1 receptors (IGF-1R) which form a signaling complex with TSHR. IGF-1R is overexpressed by orbital fibroblasts and by T cells and B cells in Graves' disease and thyroid eye disease. This activation results in inflammation, edema, tissue remodeling, and the expansion of extraocular muscle and adipose tissues.(4,5,7) Thyroid eye disease has a natural history of rapid deterioration (active phase) in which inflammation and eye manifestations are predominant, followed by a brief stabilization (static phase), and then a gradual improvement towards baseline (inactive phase) which patients usually enter between 12 to 18 months from onset.(3,7) Improvement in signs and symptoms typically occur during the inactive phase, but proptosis and extraocular muscle dysfunction do not usually normalize without intervention and can persist in up to 50% of patients.(7) The ATA recommends a multidisciplinary approach to the management of thyroid eye disease, specifically noting endocrinologists and ophthalmologists experienced in the treatment of thyroid eye disease and other specialties for consultation (e.g., ear/nose/throat, plastic surgery, radiation therapy, endocrine surgery). Of the many risk factors for the development of thyroid eye disease, only three of them are responsive to interventions; cigarette smoking, thyroid dysfunction, and the use of

radioactive iodine (RAI). Smoking can lead to the development or worsening of TED and decreases therapy efficacy. Smoking reduction or cessation is strongly recommended by the ATA, including the avoidance of second-hand smoke. Radioactive iodine therapy should be avoided in active, moderate-to-severe thyroid eye disease, and patients are at a higher risk of TED with a history of RAI within the past 6 months but can be treated with glucocorticoids for prevention. Uncontrolled hyper- or hypothyroidism can play a detrimental role in the progression of thyroid eye disease. The ATA strongly recommends achieving and maintaining euthyroidism as soon as possible.(3,7)

The ATA indicates there are two interdependent components when assessing thyroid eye disease, inflammatory activity (including pain, redness, and edema) and disease severity (including proptosis, lid malposition, exposure keratopathy, and optic neuropathy). Both components, as well as disease trend over time and impact on daily living, need to be assessed to guide management and predict outcomes.(7) The active phase is best described by the clinical activity score (CAS) with a score greater than or equal to 3 indicating active disease. The CAS consists of seven (initial evaluation) to ten (follow-up evaluations) elements.(3) Patients with multiple features of inflammation are considered to be in the active phase of the disease. A history of progressive TED may also support the presence of active disease. Repeating the assessments after 4 to 6 weeks can signify active disease if there is a measurable worsening in disease signs and symptoms.(7) Disease severity is best assessed using objective, quantifiable parameters and can help guide treatment selection. Severity is classified as patients having mild, moderate-to-severe, or sight-threatening disease.(3) TED can have a negative impact on quality of life (QoL) and daily activities, and the FDA has endorsed QoL information as a component for directing therapy. These negative effects on QoL correlate with disease activity and severity and may persist for years. The physical and psychosocial impact of TED should be assessed for each patient to guide therapeutic choices.(3,7)

The ATA and European Thyroid Association (ETA) consensus statement define activity and severity as the following:(7)

- Activity:
  - CAS greater than or equal to 3 (each item scores 1 point if present)
    - Spontaneous retrobulbar pain
    - Pain on attempted up or lateral gaze
    - Redness of the eyelids
    - Redness of the conjunctiva
    - Swelling of the eyelids
    - Inflammation of the caruncle and/or plica
    - Conjunctival edema, also known as chemosis
  - History or documentation of progression of TED based on subjective or objective worsening of vision, soft tissue inflammation, motility, or proptosis is suggestive of active TED independently of the CAS
- Severity:
  - Sight-threatening TED - patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown and/or globe subluxation
  - Moderate to severe TED - patients without sight-threatening disease whose eye disease has sufficient impact on daily life to justify the risks of medical or surgical intervention and usually have ONE or more of the following:
    - Lid retraction greater than or equal to 2 mm
    - Moderate or severe soft tissue involvement
    - Proptosis greater than or equal to 3 mm above normal for race and sex
    - Diplopia (Gorman score 2-3)
  - Mild TED - patients whose features of TED have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment and usually have one or more of the following:
    - Minor lid retraction (less than 2 mm)
    - Mild soft tissue involvement

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Proptosis less than 3 mm above normal for race and sex
Transient or no diplopia
Corneal exposure responsive to lubricants

The ATA/ETA recommend the following treatments for TED:(7)

Local ocular measures and lifestyle intervention should be offered to all patients
Mild TED: single course of selenium selenite 100 micrograms twice daily for 6 months may be considered
Moderate to severe active TED:

Intravenous glucocorticoid (IVGC) therapy is preferred when disease activity is the prominent feature in the absence of either significant proptosis* or diplopia
Rituximab or tocilizumab may be considered for TED inactivation in glucocorticoid resistant (unresponsive or intolerant) patients. Tepezza has not been evaluated in this setting.
Tepezza is preferred therapy, if available, in patients with significant proptosis* and/or diplopia
Rituximab is acceptable in patients with prominent soft tissue involvement
Radiotherapy is preferred treatment in patients whose principal feature is progressive diplopia

Sight-threatening: urgent treatment with IVGC and consideration for decompression surgery

*The ATA/ETA defines significant proptosis as proptosis greater than or equal to 3 mm above the upper limit for race and sex or proptosis less than 3 mm that has sufficient impact on daily life to justify the risks of treatment. The task force elected to avoid a numerical definition since it would exclude some patients who might otherwise benefit from therapy.
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<tr><td>Efficacy</td><td>
Tepezza was evaluated in 2 randomized, double-masked, placebo-controlled studies in 171 patients with thyroid eye disease: Study 1 (NCT01868997) and Study 2 (NCT03298867). Patients were randomized to receive Tepezza or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Inclusion criteria required patients to have a clinical diagnosis of thyroid eye disease with symptoms, and to be euthyroid or have thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Prior surgical treatment for thyroid eye disease was not permitted. Proptosis ranged from 16 to 33 mm and 125 patients (73%) had diplopia at baseline. The median age was 52 years (range 20 to 79 years) and 27% of patients were smokers at baseline.(1)
The primary outcome of both studies was proptosis responder rate at week 24, which was defined as the percentage of patients with greater than or equal to 2 mm reduction in proptosis in the study eye from baseline without deterioration (greater than or equal to 2 mm increase) in the non-study eye in proptosis.(1)
<table>
<tr><td></td><td colspan="3">Study 1</td><td colspan="3">Study 2</td></tr>
<tr><td></td><td>Teprotumumab

N=42</td><td>Placebo

N=45</td><td>Difference (95% CI)</td><td>Teprotumumab

N=41</td><td>Placebo

N=42</td><td>Difference (95% CI)</td></tr>
<tr><td>Proptosis responder rate at week 24, % (n)</td><td>71% (30)</td><td>20% (9)</td><td>51% (33, 69)</td><td>83% (34)</td><td>10% (4)</td><td>73% (59, 88)</td></tr>
<tr><td>Proptosis (mm) average</td><td>-2.5 (0.2)</td><td>-0.2 (0.2)</td><td>-2.3 (-2.8, -1.8)</td><td>-2.8 (0.2)</td><td>-0.5 (0.2)</td><td>-2.3 (-2.8, -1.8)</td></tr>
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	change from baseline through week 24, LS mean (SE)

Diplopia response was evaluated in a subgroup of patients that had diplopia at baseline in Study 1 and 2. Diplopia was assessed by categorizing patients into one of four grades, ranging from no diplopia (scored as 0) to continuous diplopia (scored as 3). Response was defined as a reduction in diplopia of one grade or more and was significantly higher in the teprotumumab group, with 53% (n=66) of patients treated with Tepezza responding compared to a 25% (n=59) response rate for patients treated with placebo (p less than 0.01).(1,4,5)

Following discontinuation of treatment in Study 1, 53% of patients (16 of 30 patients) who were proptosis responders at week 24 maintained proptosis response 51 weeks after the last Tepezza infusion. 67% of patients (12 of 18) who were diplopia responders at week 24 maintained diplopia response 51 weeks after the last Tepezza infusion.(1)

Safety	Teprotumumab has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Tepezza prescribing information. Horizon Therapeutics Ireland. July 2023.
2	American Thyroid Association. Thyroid Eye Disease (Also Known as Graves' Ophthalmopathy or Graves' Orbitopathy). (n.d.). Last updated 2022. https://www.thyroid.org/thyroid-eye-disease/
3	Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343-1421. doi:10.1089/thy.2016.0229
4	Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. The New England Journal of Medicine. 2017;376(18):1748-1761. doi:10.1056/nejmoa1614949
5	Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. The New England Journal of Medicine. 2020;382(4):341-352. doi:10.1056/nejmoa1910434
6	Reference no longer used.
7	Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. *European Thyroid Journal*. 2022;11(6). doi:10.1530/etj-22-0189

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J3241	Tepezza	teprotumumab-trbw for iv soln	500 MG	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Tepezza	teprotumumab-trbw for iv soln	500 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has a diagnosis of moderate to severe thyroid eye disease **AND** 2. The patient has ONE of the following symptoms: A. Proptosis greater than or equal to 3 mm above normal **OR** B. Proptosis less than 3 mm above normal that has sufficient impact on daily life to justify the risks of treatment **OR** C. Diplopia (Gorman score 2-3) **AND** 3. ONE of the following (lab results required): A. The patient is euthyroid (e.g., thyroid function test within normal limits) **OR** B. The patient has thyroxine (T4) and free triiodothyronine (T3) levels less than 50% above or below normal limits **AND** 4. The patient has ONE of the following: A. Clinical Activity Score (CAS) greater than or equal to 3 in the more severely affected eye(s) **OR** B. History of progression of thyroid eye disease based on subjective or objective worsening of vision, soft tissue inflammation, motility, or proptosis **AND** 5. The patient has NOT had prior surgical treatment for thyroid eye disease **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, ophthalmologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. ONE of the following: A. The patient has not been previously treated with the requested agent **OR** B. The patient has been previously treated with the requested agent AND the patient has NOT completed a full course of therapy (i.e., 8 infusions) **AND** 9. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** One treatment course per lifetime