BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 08/31/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

TEPEZZA (teprotumumab-trbw)

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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TEPEZZA (teprotumumab-trbw)

Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Tepezza (teprotumumab-trbw) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Ophthalmologist or Endocrinologist

2. Individual is 18 years of age or older

3. Individual has a diagnosis of moderate to severe Thyroid Eye Disease (TED) defined as **ONE** of the following:

   - Symptomatic, active disease (Clinical Activity Score ≥ 3) with **ONE** of the following:

     a. Lid retraction ≥ 2 mm
     b. Moderate or severe soft tissue involvement
     c. Proptosis ≥ 3 mm above normal values for race and sex
     d. Intermittent or constant diplopia

   - Stable, inactive disease (Clinical Activity Score < 3) with **ONE** of the following:

     a. Proptosis ≥ 3 mm above normal values for race and sex
     b. Proptosis ≥ 3 mm increase in proptosis from baseline (before diagnosis of TED)

4. Individual meets **ALL** of the following:

   - For individuals with diabetes, A1c is ≤ 8 percent
   - Individual is euthyroid OR has thyroxine and free triiodothyronine levels less than 50% above or below normal limits
   - Hearing evaluation has been completed and will be evaluated during and after treatment with Tepezza

5. Individual has not had prior orbital irradiation or surgery and there is no plan for corrective surgery or orbital irradiation in the future

6. Individual has not had a decrease in best corrected visual acuity due to optic neuropathy within the previous 6-months (i.e., a decrease in vision of 2 lines on the Snellen chart, new visual defect, or color defect secondary to optic nerve involvement)

7. Individual does not have corneal decompensation unresponsive to medical management (such as keratoplasty)

8. **For active TED (CAS ≥ 3):** individual has documented failure, contraindication per FDA label or intolerance to a glucocorticosteroid (IV or oral) with or without mycophenolate

9. There is no concurrent use with other biologic immunomodulators [e.g., rituximab (Rituxan and rituximab biosimilars), Actemra (tocilizumab), Kevzara (sarilumab), etc.]

Approval duration: 6 months, limited to one course per lifetime (8 infusions)

- Tepezza (teprotumumab-trbw) for all other indications not previously listed is considered ***experimental or investigational*** and will not be approved when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Tepezza (teprotumumab-trbw) is an insulin-like growth factor-1 receptor (IGF-1R) inhibitor indicated for the treatment of Thyroid Eye Disease (TED). Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling. The mechanism of action for teprotumumab-trbw in patients with TED has not been fully characterized.

TED is an inflammatory disease of the eye and the surrounding tissues. The inflammation is due to an autoimmune reaction resulting in the body's immune system attacking tissues within and around the eye socket. TED is also known as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy.

Major ocular symptoms include one or more of the following: a sense of irritation in the eyes; excessive tearing that is often made worse by exposure to cold air, wind, or bright lights; eye or retroocular discomfort or pain; blurring of vision; diplopia; and occasionally, loss of vision. The characteristic signs of Graves' orbitopathy are proptosis (in up to 60% of TED patients) and periorbital edema.

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In the majority, orbitopathy occurs in the setting of current or past Graves' hyperthyroidism (low TSH, high free thyroxine [T4] and/or triiodothyronine [T3]), but in approximately 10% of patients, Graves' thyroid disease is absent. Orbitopathy can appear before the onset of hyperthyroidism in approximately 20% of patients.

Activity of disease can be assessed by using the clinical activity score (CAS) (See Definitions section: table 1). It is useful for determining therapy and gauging response. Severity of disease is an independent measure that assesses threat to vision and the degree of proptosis and soft tissue involvement (see Definitions section: table 2). Other indices of grading the severity are available and sometimes used such as NOSPECS and the European Group of Graves' Orbitopathy (EUGOGO).

Patients with mild orbitopathy (mild chemosis, mild-to-moderate eyelid swelling, proptosis < 3 mm above upper limit of normal for race, no or intermittent diplopia, no corneal exposure responsive), local measures are usually effective in relieving eye symptoms, and no additional treatment is needed. Selenium may improve soft tissue swelling in some. Some patients with active, mild orbitopathy may need thionamides, radioiodine, or surgery.

Patients with moderate-to-severe orbitopathy, should receive initial treatment with a glucocorticoid, given either orally or intravenously depending on the severity of the disease.

If glucocorticoid therapy is contraindicated, cannot be tolerated, or is ineffective, options include other medical therapies, external orbital radiation, or orbital decompression surgery. If there is no initial response to the first few doses of glucocorticoids, and a decision is made to proceed with alternative medical therapy, choices include mycophenolate mofetil, tocilizumab, teprotumumab, or rituximab.

All patients should be advised of local measures to improve symptoms. Local measures include eye shades, artificial tears, raising the head of the bed at night, and eye patching or prisms for diplopia. Photophobia and sensitivity to wind or cold air are often relieved by use of dark glasses and instillation of artificial tears every two to three hours during the day and of lubricants, such as 1% methylcellulose drops, at night. All patients should stop smoking if applicable.

Definitions:

Table 1: Assessment of Graves' Orbitopathy (GO): Clinical Activity Score (CAS) elements:

Elements*	Each visit	Comparison with previous visit	Score
Painful feeling behind the globe over last four weeks	X		1
Pain with eye movement during last four 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 eye)	X		1
Increase in proptosis ≥ 2 mm		X	1
Decreased eye movements ≥ 5° any direction		X	1
Decreased visual acuity ≥ 1 line on Snellen chart		X	1

* A seven-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a CAS ≥ 3.

References:
1. Mourits MP, Koornneef L, Wiersinga WM, et al. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: A novel approach. Br J Ophthalmol 1989; 73:639.
2. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 1997; 47:9.

Table 2: Graves' Orbitopathy (GO) Severity Assessment:

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

Upper limits of normal:	
African American	F/M = 23/24 mm
White	F/M = 19/21 mm
Asian	F/M = 16/17 mm (Thai) or 18.6 mm (Chinese)

* Mild GO: patients whose features of GO have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment.

** Moderate-to-severe GO: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).

*** Sight-threatening GO: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.

¶ Proptosis refers to the variation compared with the upper limit of normal for each race/sex or the patient's baseline, if available.

References:
1. de Juan E Jr, Hurley DP, Sapira JD. Racial differences in normal values of proptosis. Arch Intern Med 1980; 140:1230.
2. Sarinnapakorn V, Sridama V, Sunthornthepvarakul T. Proptosis in normal Thai samples and thyroid patients. J Med Assoc Thai 2007; 90:679.

3. Tsai CC, Kau HC, Kao SC, Hsu WM. Exophthalmos of patients with Graves' disease in Chinese of Taiwan. Eye (Lond) 2006; 20:569.
4. Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid 2008; 18:333.

NOSPECS:

Class 0: **N**o signs or symptoms
Class 1: **O**nly signs (upper lid retraction)
Class 2: **S**oft tissue involvement (swelling of the eye or tissues surrounding the eye)
Class 3: **P**roptosis (bulging of the eye out of the eye socket)
Class 4: **E**xtraocular muscle involvement (usually with strabismus)
Class 5: **C**orneal involvement (severe dry eye from inability to adequately close the eye)
Class 6: **S**ight loss (due to optic nerve involvement)

Table 3: The European Group of Graves' Orbitopathy (EUGOGO):

Mild	Only a mild impact on daily life Insufficient signs/symptoms to justify immunosuppressive drugs or surgical treatment One or more of the following: Minor lid retraction (< 2mm) Mild soft tissue involvement Proptosis (bulging of the eye out of the eye socket) < 3mm above normal for race and gender Transient or no diplopia (double vision) Dry eye symptoms responsive to lubricants/ointments
Moderate-to-severe	Non sight-threatening, but has sufficient impact on daily life to justify immunosuppression or surgical intervention One or more of the following: Lid retraction ≥ 2mm Moderate or severe soft tissue involvement Exophthalmos ≥ above normal for race and gender Transient or constant diplopia
Sight-threatening	TED patients with optic neuropathy and/or corneal breakdown Warrants immediate intervention

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	08/15/24	Review with revisions: criteria (effective 10/14/24)
Pharmacy and Therapeutics Committee	08/17/23	Review with revisions
Pharmacy and Therapeutics Committee	08/18/22	Review with revisions
Medical Policy Panel	08/31/21	Approved guideline
Clinical Pharmacist	08/06/21	Development

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Coding:

HCPCS: J3241

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Resources:

Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Bartalena L, Kahaly GJ, Baldeschi L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol*. Aug 2021;185(4):G43-67. doi:10.1530/EJE-21-0479.

2. Davies TF, Burch HB. Clinical features and diagnosis of thyroid eye disease. In: Ross DS, Mulder JE (Eds). UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated October 18, 2022. Accessed on June 18, 2024.

3. Davies TF, Burch HB. Treatment thyroid eye disease. In: Ross DS, Mulder JE (Eds). UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 17, 2024. Accessed June 18, 2024.

4. Douglas RS, Couch S, Wester ST, et al. Efficacy and safety of teprotumumab in patients with thyroid eye disease of long duration and low disease activity. *J Clin Endocrinol Metab.* 2024;00(0)1-11. doi:10.1210/clinem/dgad637.

5. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382:341-52. doi:10.1056/NEJMoa1910434.

6. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017; 376(18): 1748-1761. doi:10.1056/NEJMoa1614949.

7. Tepezza (teprotumumab-trbw). Prescribing information. Horizon Therapeutics USA, Inc. 07/2023, at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed May 30, 2024.

8. Zhou X, Zhou D, Wang J, et al. Treatment strategies for Graves' ophthalmopathy: a network meta-analysis. *The British journal of ophthalmology*. Apr 2020;104(4):551–556

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html