MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

POLICY	Thyroid Disorders	**P&T DATE:**	3/19/2024
THERAPEUTIC CLASS	Endocrine Disorders	**REVIEW HISTORY** (MONTH/YEAR)	5/21, 12/20, 12/19,12/18, 9/17, 12/16, 11/15, 7/22, 3/23
LOB AFFECTED	Medi-Cal		

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the HPSJ Pharmacy and Therapeutic Advisory Committee.

Effective 1/1/2022, the Pharmacy Benefit is regulated by Medi-Cal Rx. Please visit https://medi-calrx.dhcs.ca.gov/home/ for portal access, formulary details, pharmacy network information, and updates to the pharmacy benefit.

All medical claims require that an NDC is also submitted with the claim. If a physician administered medication has a specific assigned CPT code, that code must be billed with the correlating NDC. If there is not a specific CPT code available for a physician administered medication, the use of unclassified CPT codes is appropriate when billed with the correlating NDC.

OVERVIEW

Treatment of hyperthyroidism and hypothyroidism is well-defined: methimazole and levothyroxine monotherapy are the mainstays of treatment for hyperthyroidism and hypothyroidism, respectively.[1,2] The purpose of this coverage policy is to review the available agents (Table 1) and distinguish where the medications may be billed to. For agents listed for coverage under the medical benefit, this coverage is specific to outpatient coverage only (excludes emergency room and inpatient coverage).

Table 1: Available Anti-Thyroid & Thyroid Medications *(Current as of 11/2023)*

CPT Codes	Generic Name (Brand Name)	Available Strengths	Pharmacy Benefit	Medical Benefit (Restrictions)
ANTI-THYROID MEDICATIONS				
--	Methimazole	5, 10 mg tablets	Yes	No
--	Propylthiouracil	50 mg tablet	Yes	No
THYROID MEDICATIONS				
--	Adthyza	15 mg, 16.25 mg, 30 mg, 32.5 mg, 60 mg, 65 mg, 90 mg, 97.5 mg, 120 mg, 130 mg tablets	Yes	No
--	Armour Thyroid	15, 30, 60, 90, 120, 180, 240, 300 mg tablets	Yes	No
--	Liothyronine sodium (Cytomel)	5, 25, 50 mcg tablets	Yes	No
--	Levothyroxine sodium (Euthyrox, Levoxyl)	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg tablets	Yes	No
--	Nature-Throid	48.75, 65, 81.25, 97.5, 113.75, 130, 146.25, 162.5, 195, 260, 325 mg tablets	Yes	No
--	NP Thyroid	15, 30, 60, 90,120 mg tablets	Yes	No
--	Synthroid	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets	Yes	No
--	Tirosint	13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg capsules	Yes	No
--	Unithroid	25, 50, 75, 88, 100, 112,125, 137, 150, 175, 200, 300 mcg tablets	Yes	No

--	Westhroid	32.5, 65, 97.5, 130, 195 mg tablets	Yes	No
--	WP Thyroid	16.25, 32.5, 48.75, 65, 81.25, 97.5, 113.75, 130 mg tablets	Yes	No
THYROID EYE MEDICATIONS				
J3240	Thyrotropin alfa (Thyrogen)	1.1 mg vial	Yes	Yes
J3241	Teprotumumab-trbw (Tepezza)	500 mg vials	Yes	Yes (PA, QL)

PA = Prior Authorization Required *QL = Quantity Limit*

EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for agents with medical benefit restrictions. This coverage criteria has been reviewed and approved by the HPSJ Pharmacy & Therapeutics (P&T) Advisory Committee. For agents that do not have established prior authorization criteria, HPSJ will make the determination based on Medical Necessity criteria as described in HPSJ Medical Review Guidelines (UM06).

Thyroid Agents
Teprotumumab-trbw (Tepezza)

- **Coverage Criteria:** Tepezza is reserved for patients with the following:
  - Moderate-to-severe thyroid associated orbitopathy with Clinical Activity Score for Graves Orbitopathy ≥4.
  - Failure of a 4-week trial of a systemic corticosteroid (at up to maximally indicated doses), unless clinically significant adverse effects are experienced, or all are contraindicated.
  - Patient has not had a history of surgical intervention for thyroid eye disease.
  - Patient must not have had optic nerve involvement within the last six months.
- **Limits:** Fill limit of 8 for a total of 8 doses. Must be prescribed by an endocrinologist/ophthalmologist.
- **Required Information for Approval:** Prescription history or medical authorization history showing at least a 4-week trial of glucocorticoids except if intolerable or contraindicated.
- **Other Notes:** Patient must not have planned surgical ophthalmological intervention during Tepezza use. Please note Tepezza is distributed exclusively by Accredo specialty pharmacy as a limited distribution drug.

Thyroid Agents
Thyrotropin alfa (Thyrogen)

- **Coverage Criteria:** Approval is determined by medical necessity criteria.
- **Limits:** None
- **Required Information for Approval:** N/A

CLINICAL JUSTIFICATION

Methimazole is recommended for the treatment of all patients with Graves' Disease (except during the first trimester of pregnancy), in the treatment of thyroid storm, and in patients who refuse radioactive iodine therapy or surgery.[1] During the first trimester of pregnancy, propylthiouracil is preferred because it does not cross the placenta as readily, whereas methimazole has been associated with rare birth defects.[3] Levothyroxine monotherapy is the current standard of care for treating hypothyroidism. Levothyroxine (synthetic T4) is preferred over T3 agents (desiccated thyroid extracts and liothyronine) due to its long half-life and better gastrointestinal absorption.[2]

REFERENCES

1. Bahn RS, Burch HB, Cooper DS et al. Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and the American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(3):456-520.
2. Garber JR, Cobin RH, Gharib H et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18(6):988–1028.
3. Thyroid disease in pregnancy. Practice Bulletin No. 148. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2015;125:996–1005.
4. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. N Engl J Med. 2020; 382: 341-352.
5. Douglas RS, Kahaly GJ, Ugradar S, et al. Teprotumumab Efficacy, Safety, and Durability in Longer-Duration Thyroid Eye Disease and Re-treatment: OPTIC-X Study. Ophthalmology. 2022;129(4):438-449. doi:10.1016/j.ophtha.2021.10.017
6. Bartalena L, Kahaly G, Baldeschi L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. European Journal of Endocrinology. 2021; 185(4), G43-G67
7. Burch, H. B., Perros, P., Bednarczuk, T., Cooper, D. S., Dolman, P. J., Leung, A. M., ... & Stan, M. N. (2022). Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid, 32(12), 1439-1470.
8. Tepezza prescribing information. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761143s000lbl.pdf

REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	HPSJ Coverage Policy – Endocrine Disorders – Thyroid Disorders 2015-11.docx	11/2015	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy - Endocrine Disorders - Thyroid Disorders 2016-12.docx	12/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy - Endocrine Disorders - Thyroid Disorders 2017-09.docx	9/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Endocrine – Thyroid Disorders 2018-12.docx	12/2018	Matthew Garrett, PharmD
Review Policy	Thyroid Disorders	12/2019	Matthew Garrett, PharmD
Review Policy	Thyroid Disorders	12/2020	Matthew Garrett, PharmD
Review Policy	Thyroid Disorders	5/2021	Matthew Garrett, PharmD
Reactivation of Policy	Thyroid Disorders	7/2022	Matthew Garrett, PharmD
Review of Policy	Thyroid Disorders	03/2023	Matthew Garrett, PharmD
Review of Policy	Thyroid Disorders	03/2024	Matthew Garrett, PharmD

Note: All changes are approved by the HPSJ P&T Committee before incorporation into the utilization policy

DRUG MONOGRAPH
PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

Health Plan of San Joaquin

MEDICATION:	Tepezza (Teprotumumab)	**P&T DATE:**	5/11/2021
CLASS:	Monoclonal Antibody	**REVIEW HISTORY:** (*month/year*)	
LOB:	Medi-Cal		

Monograph: Tepezza (Teprotumumab)

DRUG DESCRIPTION:

Tepezza (Teprotumumab) is a human monoclonal antibody with a novel, breakthrough mechanism. Inhibition of insulin-like growth factor-1 receptor (IGF-1R) via the IGF-1R/TSHR signaling complex at the source of the disease blocks fibroblast activation and decreases proptosis by reducing inflammation, preventing muscle and fat tissue remodeling, and preventing tissue expansion behind the eye.[1] Visual function and diplopia will also improve as a result. Tepezza became FDA approved in January of 2020 for the treatment of thyroid eye disease (TED). There are currently no documented limitations or contraindications for its use.[1] Tepezza is manufactured by Horizon Therapeutics and is available as an injection given by a healthcare provider.

INDICATIONS:

- **Thyroid Eye Disease**[1]

ADMINISTRATION, DISTRIBUTION, METABOLISM, EXCRETION (ADME)/PHARMACOKINETICS (PK)/PHARMACODYNAMICS (PD):

- **Mechanism of Action:**[1,2]
    - Targets and blocks IGF-1R to inhibit fibroblast activation by autoantibodies via the IGF-1R/TSHR signaling complex. IGF-1R belongs to a class of tyrosine kinase inhibitors. It binds to IGF1, which is a polypeptide protein hormone similar to insulin. IGF1 plays an important role in growth and can induce hypertrophy of tissues as seen in Grave's orbitopathy. Inhibition of IGF-1R and subsequently fibroblast activation results in decrease inflammation and proptosis and improvement of visual function and diplopia.
- **Dosage and Administration:**[1]
    - Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions.
    - Administer Tepezza by intravenous infusion over 90 minutes for the first two infusions.
        - If well tolerated, the minimum time can be reduced to 60 minutes.
        - If not well tolerated, the minimum time should remain at 90 minutes.
    - Do not administer as an intravenous push or bolus.
    - Do not infuse concomitantly with other agents.
- **Pharmacokinetics:**

  ADME:[1]
  - Absorption: no information available
  - Distribution: Volume of distribution (two-compartment model) – central 3.26 ± 0.87 L; peripheral 4.32 ± 0.67 L
  - $t_{1/2}$: 20 ± 5 days

- Metabolism: Expected to undergo metabolism via proteolysis
- Excretion: no information available

- **Pharmacodynamics (PD)**:[1,3]
  Renal impairment: there are no dosage adjustments provided in the manufacturer's labeling; however, there are no significant differences in the pharmacokinetics of teprotumumab in patients with CrCl ≥30 mL/minute.
  Hepatic impairment: there are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Guideline Summary:
2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis[4]

- Patients with Graves' orbitopathy (GO) should achieve euthyroidism and stop smoking if applicable.
- Active thyroid eye disease is assessed using Clinical Activity Score (CAS), a 7-point scale utilizing signs and symptoms of inflammation, and severity is assessed using Graves' Orbitopathy Severity Assessment, which provides objective and quantifiable parameters

TABLE 12. ASSESSMENT OF GRAVES' ORBITOPATHY: CLINICAL ACTIVITY SCORE ELEMENTS[a]

Elements[b]	*Each visit*	*Comparison with previous visit*	*Score*
Painful feeling behind the globe over last 4 weeks	X		1
Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (flesh body at medial angle of 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]Sources: Adapted from Mourits *et al.* (523,524).
[b]A 7-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a clinical activity score (CAS) ≥3.

TABLE 13. GRAVES' ORBITOPATHY SEVERITY ASSESSMENT[a]

Grade[b]	*Lid retraction*	*Soft tissues*	*Proptosis*[c]	*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)				

[a]Sources: Adapted from de Juan *et al.* (676), Sarinnapakorn *et al.* (677), Tsai *et al.* (678), and Bartalena *et al.* (525).
[b]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.
[c]Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

- Treatment varies depending on the severity of their eye disease:
  - For mild disease with no symptom progression, local measures such saline eye drops often lead to sufficient relief without requiring additional treatment.
  - For moderate-to-severe disease or symptom progression, initial treatment with glucocorticoids is recommended. Oral formulation may be indicated for patients with moderate disease while IV formulation may be preferred in severe or progressive cases.
  - For patients with sight-threatening disease, immediate IV glucocorticoid therapy should be administered, and admit the patient for possible urgent orbital decompression surgery.

- Selection of secondary therapies is limited in current guidelines.
- Other approaches include surgery or orbital radioiodine, but the latter is contraindicated in patients with moderate-to-severe or sight-threatening disease.

2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy[5]

- All patients with Graves' hyperthyroidism, regardless of presence or absence of GO, should refrain from smoking and promptly restore euthyroidism.
- Oral prednisone prophylaxis is recommended in radioiodine-treated patients at high risk of progression or de novo development of GO (starting dose of 0.3-0.5 mg/kg/day).
- Mild GO should be treated with local treatments and general measures to control risk factors.
    - If impact of disease on QoL outweighs risks, then immunosuppressive therapy for active GO or rehabilitative surgery for inactive GO may be justified.
    - A 6-month course of selenium supplementation should be given as it improves eye manifestations and QoL while preventing GO progression to more severe forms.
- Moderate-to-severe and active GO should be treated with intravenous glucocorticoid as the first line.
    - Intermediate dose regimens are recommended for most patients within this spectrum.
    - High dose regimens should be reserved for the worst cases within this spectrum.
- Sight-threatening GO should be immediately treated with very high doses of IV glucocorticoids and an urgent orbital decompression should be performed if response is absent or poor within 2 weeks.
    - If resolved or improved, pulses of weekly IV glucocorticoids should be continued as described in the management of moderate-to-severe and active GO.

Neither guidelines have made a recommendation for or against the use of Tepezza since it was FDA approved after current guidelines were created. However, it has shown significant efficacy when compared to placebo in two randomized clinical trials.

Inclusion/Exclusion:

Clinical Trial	Inclusion	Exclusion
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[6]	1. Clinical diagnosis of Graves' disease associated with active TED and a clinical activity score of ≥ 4 2. Fewer than 9 months from onset of TED 3. No previous medical or surgical treatment, excluding local supportive measures and oral steroids if the maximum cumulative dose is less than 1000 mg methylprednisolone or equivalent with at least 6 weeks between last administration of oral steroids and randomization 4. Euthyroid or with mild hypo or hyperthyroidism defined as free thyroxine (FT4) and free triiodothyronine (FT3) levels less than 50% above or below the normal limits (every effort should be made to correct the mild hypo- or hyperthyroidism promptly)	1. Optic neuropathy 2. Corneal decompensation unresponsive to medical management 3. Oral or IV steroid treatment for any non-TED reason in the preceding 3 months 4. Poorly controlled diabetes 5. Platelets <100 x 10^9/L 6. Hgb concentration >2 g/dL below the lower limit of normal
Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. *N Engl J Med*. 2020;382(4):341-352. doi:10.1056/NEJMoa1910434[7]	1. Written informed consent 2. Male or female participant between the ages of 18 and 80 years, inclusive, at Screening 3. Clinical diagnosis of Graves' disease associated with active TED with a Clinical Activity Score (CAS) ≥ 4 (on the 7-item scale) for the most severely affected eye at Screening and Baseline 4. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia 5. Onset of active TED symptoms (as determined by participant records) within 9 months prior to Baseline 6. Participants must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels < 50% above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial 7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study	1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months 2. Corneal decompensation unresponsive to medical management 3. Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline 4. Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline 5. Previous orbital irradiation or surgery for TED 6. Any steroid use (intravenous [IV] or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if the corticosteroid was discontinued at least 4 weeks prior to Screening 7. Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids are allowed) 8. Selenium and biotin must be discontinued 3 weeks prior to Screening and must not be restarted during the clinical trial; however, taking a multivitamin that includes selenium and/or biotin is allowed

8. Alanine aminotransferase (ALT) or AST ≤ 3 times the upper limit of normal (ULN) or serum creatine <1.5 times the ULN according to age at Screening
9. Diabetic participants must have well-controlled stable disease (defined as HbA1C < 9.0% with no new diabetic medication [oral or insulin] or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening)
10. Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and through Week 48 of the Follow-Up Period); participants who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate less than 1% per year) when used consistently and correctly, includes implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomized partner
11. Male participants must be surgically sterile or, if sexually active with a female partner of childbearing potential, must agree to use barrier contraceptive method from Screening through 180 days after the last dose of study drug
12. Participant is willing and able to comply with the study protocol and evaluations for the duration of the study

9. Any previous treatment with rituximab or tocilizumab. Use of any other non-steroid immunosuppressive agent within 3 months prior to Screening
10. Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude study participation or complicate interpretation of study results.
12. Bleeding diathesis that in the judgment of the Investigator would preclude inclusion in the clinical trial
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin)
14. Pregnant or lactating women
15. Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the participant
16. Biopsy-proven or clinically suspected inflammatory bowel disease
17. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to mAbs
18. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study
19. Previous enrollment in this study or participation in a prior teprotumumab clinical trial
20. Human immunodeficiency virus (HIV), hepatitis C or hepatitis B infections.

Evidence Review (Safety/Efficacy):

<table>
<tr><th>Clinical Trial</th><th>Efficacy</th><th>Safety</th></tr>
<tr>
<td>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 [6]</td>
<td>
(n=88, 87 completed study)
Phase II study involving patients with active, moderate-to-severe ophthalmopathy
Randomization 1:1 teprotumumab, placebo
24-week treatment, total of 8 infusions (once every 3 weeks)
<table>
<tr><th>Result (24 weeks)</th><th>Teprotumumab</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>Primary Endpoint: responder status at week 24 (reduction of ≥2 points in the Clinical Activity Score and reduction of ≥2 mm in proptosis)</td><td>69%</td><td>20%</td><td>≤0.001</td></tr>
<tr><td>Secondary Endpoint: overall average change in GO-QOL scale (combined) from baseline to week 24</td><td>17.7±2.4</td><td>6.8±2.3</td><td>≤0.01</td></tr>
<tr><td>Secondary Endpoint: overall average change in proptosis from baseline to week 24</td><td>-2.46±0.20</td><td>-0.15±0.19</td><td>≤0.001</td></tr>
<tr><td>Secondary Endpoint: overall average change in Clinical Activity Score from baseline to week 24</td><td>-3.43±0.18</td><td>-1.85±0.17</td><td>≤0.001</td></tr>
<tr><td>Secondary Endpoint: overall average change in GO-QOL scale (visual functioning) from baseline to week 24</td><td>21.7±2.9</td><td>7.5±2.7</td><td>≤0.001</td></tr>
<tr><td>Secondary Endpoint: overall average change in GO-QOL scale (appearance) from baseline to week 24</td><td>12.9±2.8</td><td>6.6±2.7</td><td>0.1</td></tr>
</table>
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<table>
<tr><th colspan="3">Adverse Events (up to week 72)</th></tr>
<tr><th>Result</th><th>Teprotumumab</th><th>Placebo</th></tr>
<tr><td>Serious adverse events</td><td>11.63%</td><td>2.27%</td></tr>
<tr><td>Muscle spasm</td><td>18.6%</td><td>4.55%</td></tr>
<tr><td>Nausea</td><td>18.6%</td><td>9.09%</td></tr>
<tr><td>Alopecia</td><td>6.98%</td><td>4.55%</td></tr>
<tr><td>Diarrhea</td><td>11.63%</td><td>4.55%</td></tr>
<tr><td>Fatigue</td><td>6.98%</td><td>13.64%</td></tr>
<tr><td>Hyperglycemia</td><td>11.63%</td><td>4.55%</td></tr>
<tr><td>Hearing impairment</td><td>6.98%</td><td>0%</td></tr>
<tr><td>Dysgeusia</td><td>6.98%</td><td>0%</td></tr>
<tr><td>Headache</td><td>6.98%</td><td>4.55%</td></tr>
<tr><td>Dry skin</td><td>6.98%</td><td>0%</td></tr>
<tr><td>Paresthesia</td><td>6.98%</td><td>0%</td></tr>
<tr><td>Rash</td><td>6.98%</td><td>9.09%</td></tr>
<tr><td>Weight decreased</td><td>6.98%</td><td>0%</td></tr>
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Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. *N Engl J Med*. 2020;382(4):341-352. doi:10.1056/NEJMoa1910434[7]

(n=83, 79 completed study)
Phase III study involving patients with active, moderate-to-severe thyroid eye disease
Randomization 1:1 teprotumumab, placebo
24-week treatment, total of 8 infusions (once every 3 weeks)

Result (24 weeks)	**Teprotumumab**	**Placebo**	**p-value**
Primary Endpoint: proptosis response at week 24 (reduction ≥2 mm)	82.9%	9.5%	<0.001
Secondary Endpoint: % of overall responders at week 24	78%	7.1%	<0.001
Secondary Endpoint: % of Clinical Activity Scale responders at week 24	58.5%	21.4%	<0.001
Secondary Endpoint: change from baseline in proptosis to week 24	-2.82±0.19	-0.54±0.19	<0.001
Secondary Endpoint: % of diplopia responders at week 24	67.9%	28.6%	<0.001
Secondary Endpoint: change from baseline in GO-QOL (combined) to week 24	13.79±2.07	4.43±2.1	<0.001

Adverse Events (up to week 24)		
Result	**Teprotumumab**	**Placebo**
Serious adverse events	4.88%	2.38%
Diarrhea	9.76%	11.9%
Nausea	14.63%	9.52%
Stomatitis	7.32%	2.38%
Fatigue	12.2%	2.38%
Muscle spasm	31.71%	9.52%
Dizziness	7.32%	0%
Dysgeusia	9.76%	0%
Headache	9.76%	9.52%
Amenorrhea	7.32%	0%
Alopecia	19.51%	11.9%
Dry skin	9.76%	0%

Black Box Warnings
None

Adverse Reaction >5%[1]
Muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin

Warnings and Precautions[1]
Infusion Reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management
Preexisting Inflammatory Bowel Disease: Monitor patients with preexisting IBD for flare of disease; discontinue Tepezza if IBD worsens
Hyperglycemia: Monitor glucose levels in all patients; treat hyperglycemia with glycemic control medications

Cost Analysis[3,8] (using average weight of 80 kg)	
Pharmacy benefit	**Medical benefit**
AWP: $17,880 per 500 mg	Unit value: $320.34 per 10 mg
Cost of initial dose: $35,760 (2 vials)	Cost of initial dose: $32,034 (2 vials)
Cost of full treatment: $536,400 (30 vials)	Cost of full treatment: $480,510 (30 vials)

Discussion:[6,7,9]

Tepezza (Teprotumumab) has shown to be effective and safe in patients with Graves' disease associated with active thyroid eye disease (TED) in two trials for FDA approval in January 2020. The first (NCT01868997), a phase II, double blind, placebo-controlled RCT included patients with active, moderate-to-severe ophthalmopathy. The primary outcome showed that teprotumumab was more effective than placebo at reducing proptosis and the Clinical Activity Score, a 7-point scale utilizing signs and symptoms of inflammation to detect active TED. Therapeutic effects were achieved quickly. By week 6, 43% of patients in the teprotumumab group and 4% of patients in the placebo group had a response ($p<0.001$), which was defined as a reduction of ≥2 points in the Clinical Activity Score and reduction of ≥2 mm in proptosis. At week 24, 69% of patients in the teprotumumab group and 20% of patients in the placebo group had a response ($p<0.001$). All secondary endpoints were statistically significant except the Graves' Orbitopathy Quality of Life (GO-QOL) appearance subscale, a questionnaire about the patients' assessment of themselves, although it had a consistent upward trend. OPTIC (NCT03298867), a phase III, double blind, placebo-controlled RCT also included patients with active, moderate-to-severe TED. Teprotumumab showed a statistically significant improvement with proptosis at week 24 than placebo (teprotumumab 82.9%, placebo 9.5%; $p<0.001$) and all secondary endpoints reached statistical significance. Limitations of both trials include lack of long-term follow up. In addition, both trials only enrolled patients with active moderate-to-severe disease, so the potential of teprotumumab in patients with milder, less active, or stable disease was not accessed. However, results of these trials suggest teprotumumab is efficacious in Graves' disease associated with TED.

Aside efficacy, safety was also monitored in both RCTs. Adverse events that occurred in more than 5% of patients in the teprotumumab group than in the placebo group were mostly mild in nature and involved no intervention or discontinuation of therapy. One adverse event of note in particular was hyperglycemia, which investigators identified as related to teprotumumab by monitoring patients' blood glucose and glycated Hgb levels. Therefore, patients with diabetes should be under glycemic control prior to starting this medication and close monitoring of an endocrinologist or ophthalmologist throughout the duration of treatment. Serious adverse events were reported in 5 of 42 patients in the teprotumumab group of the first trial, in which two involved more severe diarrhea and mental confusion, respectively, that were possibly related to the drug and three were categorized as unrelated. On the other hand, the OPTIC trial reported serious adverse events in 2 of 41 patients, which included pneumothorax, subsequently classified as probably unrelated, and infusion-related reaction, leading to withdrawal from the trial. No deaths were reported in either trials.

Neither the most recent 2016 guideline from the American Thyroid Association nor the 2016 guideline from the European Thyroid Association has made a recommendation for or against the use of teprotumumab since it became FDA approved later on. In general, both guidelines recommend achieving euthyroid status and smoking cessation. For pharmacologic treatment, mild GO patients should be treated with local measures and risk factor control while moderate-to-severe and active GO patients should be managed with glucocorticoids. Improvement usually occurs within four weeks of use. IV glucocorticoids should be administered immediately in patients with sight-threatening disease and undergo possible orbital decompression surgery. Orbital radioiodine is also an option but is contraindicated in patients with active moderate-to-severe or sight-threatening disease. From the results of two randomized clinical trials, teprotumumab would be beneficial in patients with moderate-to-severe thyroid associated orbitopathy with Clinical Activity Score ≥4 after failure of a 4-week trial with glucocorticoids. Patients must not have a history of surgical intervention for thyroid eye disease or optic nerve involvement within the last six months.

Recommendation: Add Tepezza (teprotumumab) to the formulary with the following criteria:

Coverage Criteria: Tepezza is reserved for patients with the following:

- Moderate-to-severe thyroid associated orbitopathy with Clinical Activity Score for Graves Orbitopathy ≥4.
- Failure of a 4-week trial of a systemic corticosteroid (at up to maximally indicated doses), unless clinically significant adverse effects are experienced, or all are contraindicated.
- Patient has not had a history of surgical intervention for thyroid eye disease.
- Patient must not have had optic nerve involvement within the last six months.

Limits: Fill limit of 8 for a total of 8 doses. Must be prescribed by an endocrinologist/ophthalmologist.

Required Information for Approval: Prescription history or medical authorization history showing at least a 4-week trial of glucocorticoids except if intolerable or contraindicated.

Other Notes: Patient must not have planned surgical ophthalmological intervention during Tepezza use. Please note Tepezza is distributed exclusively by Accredo specialty pharmacy as a limited distribution drug.

References:

1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.
2. Database GCHG. IGF1R Gene (Protein Coding). GeneCards. https://www.genecards.org/cgi-bin/carddisp.pl?gene=IGF1R. Accessed April 10, 2021.
3. Teprotumumab (Lexi-Drugs). http://online.lexi.com.tjlsophs.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/6912183. Accessed April 13, 2021.
4. 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
5. Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J*. 2016;5(1):9-26. doi:10.1159/000443828
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. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. *N Engl J Med*. 2020;382(4):341-352. doi:10.1056/NEJMoa1910434
8. Medi-Cal Rates. Medi-Cal. https://files.medi-cal.ca.gov/Rates/RatesHome.aspx. Accessed April 14, 2021.
9. Penta L, Muzi G, Cofini M, Leonardi A, Lanciotti L, Esposito S. Corticosteroids in Moderate-To-Severe Graves' Ophthalmopathy: Oral or Intravenous Therapy?. *Int J Environ Res Public Health*. 2019;16(1):155. Published 2019 Jan 8. doi:10.3390/ijerph16010155