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Thyroid Eye Disease Medical Drug Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent(s)	Indication(s)	Dosage
Tepezza™ (teprotumumab-trbw) Injection powder	Treatment of thyroid eye disease	10 mg/kg IV followed by 20 mg/kg every 3 weeks for 7 additional infusions

CLINICAL RATIONALE

Thyroid eye disease, also known as Graves' eye disease or Graves' ophthalmopathy, typically develops in patients with overactive thyroids. Over 50% of patients with Graves' disease go on to develop eye symptoms, which are generally mild and treatable. Symptoms can begin within 6 months 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. Decreased eye movement and eyelids, incomplete closure of the eye with corneal ulceration, compression of the optic nerve, and rarely loss of vision can occur in more advanced eye disease.[2] The presumed mechanism behind the development of thyroid eye disease is the activation of orbital fibroblasts by Graves' associated autoantibodies. This activation leads to the release of T-cell chemoattractants, initiating an interaction that leads to swelling, congestion and connective tissue remodeling. This causes extraocular muscle enlargement and orbital fat expansion.[4]

The American Thyroid Association (ATA) notes that 90% of patients that develop thyroid eye disease have a current diagnosis of or history of Graves' disease. Thyroid eye disease has a natural history of rapid deterioration followed by gradual improvement towards baseline. 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). The active phase is best described by the clinical activity score (CAS) with a score ≥3 indicating active disease. The CAS elements consist of seven (initial evaluation) to ten (follow-up evaluations) elements. Some of the eye changes seen in hyperthyroidism are due to excess thyroid hormone, such as lid retraction or stare, and when present without associated eye changes, are not considered to be thyroid eye disease.[3]

The ATA recommends assessing disease severity using objective, quantifiable parameters and should be used to direct therapy. Disease severity is described as mild, moderate to severe, and sight threatening. The European Group on Graves' Orbitopathy severity assessment elements, recommended by ATA, include the following:[3]

- Lid retraction (<2 mm for mild disease, ≥2 mm for moderate to severe disease)
- Soft tissues (corresponding mild, moderate, severe involvement)
- Proptosis (<3 mm for mild disease, ≥3 mm for moderate to severe disease)
- Diplopia (transient or absent for mild, inconstant for moderate, and constant for severe disease)
- Corneal exposure (absent for mild, mild for moderate to severe disease)
- Optic nerve status (normal for mild, moderate, and severe disease)

- Sight threatening thyroid eye disease is defined as having severe corneal exposure and optic nerve compression

There are a number of risk factors for the development of thyroid eye disease. Only three of the risk factors are responsive to interventions. Smoking and radioactive iodine therapy increase progression of thyroid eye disease and decrease therapy efficacy. Uncontrolled hyperthyroid or hypothyroid play a detrimental role in the development of thyroid eye disease. The ATA strongly recommends achieving euthyroidism as soon as possible and maintained in patients with continued hyperthyroidism or in patients with risk factors for developing thyroid eye disease.[3]

The American Academy of Ophthalmology (AAO) notes diagnosis is based on a combination of characteristic ocular abnormalities and hyperthyroidism. The typical signs of thyroid eye disease include the following:[4]

- Lid retraction
- Lid lag of the upper eyelid on downward gaze (i.e., Von graefe sign) and lid edema
- Unilateral or bilateral axial proptosis (abnormal protrusion or displacement of the eye) with increased resistance to retropulsion. Hertel's exophthalmometer is used to measure level of proptosis.
- Deep injection of bulbar conjunctiva (i.e., Goldzeiher sign)
- Extraocular muscle involvement (leading to ocular misalignment, diplopia, inability to look up when eye is adducted [i.e., elevator palsy])
- Compressive optic neuropathy is an ocular emergency

The AAO also note that the following indications that simulate thyroid eye disease need to be ruled out:[4]

- Orbital pseudotumor
- Carotid cavernous fistula
- Inflammatory orbitopathy (e.g., granulomatosis with polyangiitis)
- Orbital myositis
- Orbital tumors
- IgG4 disease

The AAO recommends the following treatment approach to thyroid eye disease:[4]

- Conservative therapies:
  - Smoking cessation
  - Achieving euthyroid status
  - Lubricants, taping, and protective shields for corneal exposure
  - Fresnel prisms or occlusion therapy for diplopia
  - Lifestyle modifications
  - Oral NSAIDs for periocular pain
- Systemic steroids:
  - Oral: dose of 1 to 1.5 mg/kg prednisone for a maximum of 2 months to decrease orbital inflammation
  - IV: pulse methylprednisolone considered an alternative to oral prednisone
- Orbital radiation: alone or in conjunction with corticosteroids at a dose of 2000 cGy for each orbit (200 cGy/day over 10 days)
- Orbital decompression: partial removal of bony walls and periosteum
- Strabismus surgery: for the treatment of significant strabismus and should be considered only after orbital decompression is complete and muscle alignment stabilized
- Teprotumumab is the first FDA approved prescription treatment for thyroid eye disease, but its place in therapy has not been established

Efficacy[1,5]
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 were: patients had a clinical diagnosis of Thyroid Eye Disease with symptoms and were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits, ophthalmopathy that had been diagnosed no more than 9 months after the onset of symptoms, Clinical Activity Score (CAS) of 4 or more in the more severely affected eye. 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. A total of 84 patients were randomized to Tepezza and 87 patients were randomized to placebo. The proptosis responder rate at week 24 was defined as the percentage of patients with ≥2 mm reduction in proptosis in the study eye from baseline, without deterioration in the non-study eye (≥2 mm increase) in proptosis. Additional evaluations included signs and symptoms of Thyroid Eye Disease including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness, chemosis, inflammation, clinical activity score and assessments of functional vision and patient appearance.

	Study 1			Study 2		
	Teprotumumab N=42	Placebo N=45	Difference (95% CI)	Teprotumumab N=41	Placebo N=42	Difference (95% CI)
Proptosis responder rate at week 24, %	71% (30)	20% (9)	51% (33, 69)	83% (34)	10% (4)	73% (59, 88)
Proptosis (mm) average change from baseline through week 24. LS mean (SE)	-2.5 (0.2)	-0.2 (0.2)	-2.3 (-2.8, -1.8)	-2.8 (0.2)	-0.5 (0.2)	-2.3 (-2.8, -1.8)

Diplopia (double vision) was evaluated in a subgroup of patients that had diplopia at baseline in Study 1 and 2, with 53% (35 out of 66 patients) response rate for patients treated with Tepezza vs 25% (15 out of 59 patients) response rate for patients treated with placebo. 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.

Safety[1]
Teprotumumab has no FDA labeled contraindications for use.

References

1. Tepezza prescribing information. Horizon Therapeutics Ireland. January 2020.
2. American Thyroid Association. Graves' Eye Disease. (n.d.). Last updated 2016. Accessed February 2021, from https://www.thyroid.org/graves-eye-disease/.
3. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Douglas S. Ross, Henry B. Burch, et. al. Thyroid 2016 26:10, 1343-1421.
4. Durairaj, V. D., MD, Gandhi, R., MD, et.al. (2019, November 10). Thyroid Ophthalmopathy. Last updated November 2020. Accessed February 2021, from https://eyewiki.org/Thyroid_Ophthalmopathy.
5. Douglas RS, Kahaly GJ, Patel A, et. al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. N Engl J Med. 2020 Jan 23;382(4):341-352. doi: 10.1056/NEJMoa1910434.

Thyroid Eye Disease Medical Drug Criteria

TARGET AGENT(S)
Tepezza™ (teprotumumab-trbw)

Brand (generic)	GPI	Multisource Code	HCPCS/ J Code
Tepezza (teprotumumab-trbw)			
500 mg vial	30192070402120	M, N, O, or Y	J3241

CRITERIA FOR APPROVAL
Evaluation
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 also has a diagnosis of Graves' disease
   AND
3. The patient's diagnosis of thyroid eye disease was made ≤9 months after onset of symptoms
   AND
4. ONE of the following (lab results required):
   a. The patient is euthyroid
      OR
   b. The patient has thyroxine and free triiodothyronine levels less than 50% above or below normal limits
   AND
5. The patient has a Clinical Activity Score (CAS) ≥4 in the more severely affected eye(s)
   AND
6. The patient has NOT had prior surgical treatment for thyroid eye disease
   AND
7. The patient does NOT have any of the following:
   a. Optic neuropathy
   b. Severe ocular surface damage
   c. Orbital pseudotumor
   d. Carotid cavernous fistula
   e. Inflammatory orbitopathy (e.g., granulomatosis with polyangiitis)
   f. Orbital myositis
   g. Orbital tumors
   h. IgG4 disease
   AND
8. ONE of the following:
   a. The patient has tried and had an inadequate response to at least ONE systemic corticosteroid used in the treatment of thyroid eye disease
      OR
   b. The patient has an intolerance or hypersensitivity to systemic corticosteroid therapy
      OR
   c. The patient has an FDA labeled contraindication to ALL systemic corticosteroids
   AND

9. 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
10. The patient does NOT have any FDA labeled contraindications to the requested agent
    AND
11. 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
12. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: One treatment course per lifetime