INPHARMD™ **MONOGRAPHS**

Tepezza®

(Teprotumumab-trbw)

The latest evidence on drug efficacy & recommendations.

InpharmD™

UPDATED MARCH 2024

OVERVIEW

REGIMEN

Generic Name	Teprotumumab-trbw
Trade Name	Tepezza®
Manufacturer	Horizon Therapeutics Ireland DAC
FDA Approval	January 21, 2020
Dosage	Initial: 10 mg/kg Maintenance: 20 mg/kg every 3 weeks for 7 additional infusions
Therapeutic Class	IGFR-1 antagonist (EENT Drug)

Indications

Treatment of thyroid eye disease (regardless of thyroid eye disease activity or duration))

PHARMACOLOGY

Teprotumumab-trbw's mechanism of action in patients with thyroid eye disease has not been fully characterized. Teprotumumab-trbw binds to insulin-like growth factor 1 receptor (IGF-1R) and blocks its activation and signaling.

PHARMACODYNAMICS

No formal pharmacodynamic studies have been conducted with teprotumumab-trbw.

PHARMACOKINETICS

Absorption/Onset:

AUC: 138 mg*hr/mL

Cmax: 632 mcg/mL

Ctrough: 176 mcg/mL

Distribution:

Central: 3.26 L

Peripheral: 4.32 L

Metabolism: Metabolism of teprotumumab-trbw has not been fully characterized. However, teprotumumab-trbw is expected to undergo metabolism via proteolysis.

Half-life Elimination: 20 days

Excretion:

Clearance: 0.27 L/day

CLINICAL DATA OVERVIEW

N = 88 • Smith et al., 2017 • Multicenter, double-masked, randomized, placebo-controlled, phase 2 trial

POPULATION

Objective: To determine the efficacy and safety of teprotumumab in patients with active, moderate-to-severe ophthalmopathy

N= 88

Placebo (n= 44)

Teprotumumab (n= 43)

METHODS

Inclusion/ exclusion criteria: Age 18 to 75 years, ophthalmopathy diagnosed no more than 9 months after onset of symptoms, Clinical Activity Score (CAS) of 4 or more on 7-point scale in more severely affected eye, not received surgical or medical treatment, with exception of oral glucocorticoids

Intervention: Patients were randomized (1:1) to receive teprotumumab IV 10 mg/kg followed by 20 mg/kg every 3 weeks for a total of eight infusions versus matched controls who received 0.9% sodium chloride.

Duration:

Intervention: 24 weeks

Follow-up: 48 weeks

METHODS

Primary outcome:
Response at week 24: teprotumumab 69% vs placebo 20% ($p<0.001$)

Secondary outcomes:
Response at week 6: 43% vs 4% ($p<0.001$)

Change from baseline in CAS: -3.43 vs -1.85 ($p<0.001$)

Safety outcomes:
Adverse events (AE)s: nausea (19% vs 9%), muscle spasms (19% vs 5%), diarrhea (14% vs 5%), hyperglycemia (12% vs 5%), hearing impairment (7% vs 0)

Serious AEs: 12% vs. 2%

CONCLUSIONS

Conclusion: A 24-week course of teprotumumab therapy provided clinical benefit in patients with active, moderate-to-severe thyroid-associated ophthalmopathy by reducing proptosis and the Clinical Activity Score and by improving the patients' quality of life.

Critique: This trial only enrolled patients with active disease of recent onset, limiting generalizability to patients with long-term disease who have exhausted other therapy options or for patients with milder, less active, or stable disease.

N = 83 • Douglas et al., 2020 • Randomized, double-blind, placebo-controlled, phase 3 multicenter trial (OPTIC)

POPULATION

Objective: To investigate the efficacy and safety of teprotumumab as compared with placebo in patients with clinically active thyroid eye disease

N= 83

Placebo (n= 42)

Teprotumumab (n= 41)

METHODS

Inclusion/ exclusion criteria: Age 18 to 75 years, ophthalmopathy diagnosed no more than 9 months after onset of symptoms, CAS of 4 or more on 7-point scale in more severely affected eye, not received surgical or medical treatment, with exception of oral glucocorticoids

Intervention: Patients were randomized (1:1) to receive either teprotumumab IV 10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions or matching placebo once every 3 weeks for 21 weeks.

Duration:

Intervention: 24 weeks

Follow-up: 48 weeks

RESULTS

Primary outcome:
Proptosis response at week 24: teprotumumab 83% vs placebo 10% (95% confidence interval [CI] 59 to 88); p<0.001)

Secondary outcomes:
Overall response at week 24: 78% vs 7% (95% CI 56 to 86); p<0.001

CAS of 0 or 1 at week 24: 59% vs 21% (95% CI 17 to 55); p<0.001

Mean change in proptosis from baseline through week 24: -2.82 mm vs -0.54 mm (95% CI -2.77 to -1.80); p<0.001

Diplopia response at week 24: 68% vs 29% (95% CI 16 to 63); p= 0.001

Mean change in Graves' ophthalmopathy-specific quality-of-life (GO-QOL) score from baseline to week 24: 13.79 vs 4.43 (95% CI 4.08 to 14.64); p<0.001

Safety outcomes:
Most of the adverse events that occurred during this period were of grade 1 or 2.

Most of the adverse events that occurred during this period were of grade 1 or 2. Potential infusion reactions were noted in six patients in the teprotumumab group and in four patients in the placebo group. Two of these

CONCLUSIONS

Conclusion: Among patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, Clinical Activity Score, diplopia, and quality of life than placebo; serious adverse events were uncommon.

Critique: This trial did not have a long-term follow-up, limiting conclusions regarding the long-term safety and efficacy of teprotumumab.

events were considered to be infusion reactions to teprotumumab.

Adverse events of special interest that occurred in less than 5% of the patients in either trial group within 21 days after the last dose included the development of hyperglycemia in two patients (<5%) in the teprotumumab group (both cases were mild). Hearing impairment was reported in five patients in the teprotumumab group: two had hypoacusis, which resolved; one had deafness, which resolved; one had autophony (bilateral intermittent echoing of the patient's own voice that occurred in conjunction with sore throat), which resolved; and one had mild patulous eustachian tube, which resolved. No auditory issues occurred in the placebo group.

No deaths occurred. Two serious adverse events occurred in the teprotumumab group: pneumothorax and infusion reaction

N = 51 • Douglas et al., 2021 • Open-label extension of OPTIC (OPTIC-X)

METHODS

Inclusion/ exclusion criteria: Placebo- and teprotumumab-treated proptosis nonresponders in OPTIC trial (< 2 mm decrease in study eye at study week 24)

Intervention: Patients who completed the original OPTIC study were enrolled into the OPTIC-X open-label extension study to receive eight infusions of teprotumumab (10 mg/kg first infusion, 20 mg/kg remaining seven infusions) every 3 weeks.

Duration: 48 weeks after initial treatment (ending on study week 72)

METHODS

Primary outcome:
Proptosis response at week 24: 89%
Median time to proptosis response: 6.4 weeks

Secondary outcomes:
Mean change from baseline at week 24 in proptosis: -3.5 mm

CAS of 0 or 1 at week 24 for patients entering study with CAS >1: 65.6%

Mean change from baseline in GO-QOL visual functioning and appearance subscales: 11.7 and 15.1, respectively

Safety outcomes: All AEs were mild or moderate, and no patients experienced a serious AE. Three patients experienced potential infusion reactions (includes AEs that occur within 2 hours after infusion initiation) characterized as dysgeusia during multiple infusions in 1 patient, generalized pruritus during the second infusion in 1 patient, and hypertension after infusion in 1 patient. All 3 patients completed the course of therapy.

Hearing impairment was reported in 4 patients as mild AEs: 2 patients with hypoacusis that resolved, 1 patient with tinnitus that resolved, and 1 patient with tinnitus that continued at last visit and was accompanied by muscle spasms (bilateral lower leg) of moderate severity that led to treatment discontinuation after the sixth infusion.

CONCLUSIONS

Conclusion: Patients with TED of longer disease duration responded similarly to those treated earlier in the disease course. Patients with an insufficient initial response or flare may benefit from additional teprotumumab therapy. No new safety risk was identified; however additional postmarketing pharmacovigilance is ongoing.

Critique: The comparative efficacy or safety of teprotumumab to other therapies for TED is unknown following the results of this study.

N = 448 • Hu et al., 2023 • Meta-analysis

POPULATION

Objective: To objectively compare the efficacy and safety of intravenous monoclonal antibodies for treatment of Graves' ophthalmopathy

N= 12 trials (448 participants)

METHODS

Literature search parameters: To identify eligible trials, references published before September 2022 were electronically searched in PubMed, Web of Science, PubMed, Embase, Cochrane Library, CBM, CNKI, Wan-Fang and ICTRP databases.

Comparisons: teprotumumab vs tocilizumab vs rituximab

Outcomes: response rate, disease inactivation rate, reduction in proptosis, improvement in diplopia from baseline to end of follow-up, and tolerability

METHODS

Results:

Response rate:
- Teprotumumab: odds ratio (OR) 0.75 (95% CI 0.66 to 0.83); p= 0.60
- Tocilizumab: OR 0.95 (95% CI 0.91 to 0.99) p= 0.34
- Rituximab: OR 0.68 (95% CI 0.46 to 0.89) p<0.01

Disease inactivation rate:
- Teprotumumab: OR 0.64 (95% ci 0.55 to 0.74); p= 0.61
- Tocilizumab: OR 0.89 (95% CI 0.8 to 0.98); p<0.01
- Rituximab: OR 0.74 (95% CI 0.52 to 0.96); p<0.01

Reduction in proptosis:
- Teprotumumab: OR 0.47 (95% CI 0 to 1.00); p<0.01
- Tocilizumab: OR 0.61 (95% CI 0.3 to 0.91); p<0.01
- Rituximab: OR 0.15 (95% CI 0 to 0.35); p<0.01

Improvement in diplopia:
- Teprotumumab: OR 0.68 (95% CI 0.58 to 0.77); p= 0.93
- Tocilizumab: OR 0.38 (95% CI 0.13 to 0.66); p<0.01
- Rituximab: OR 0.05 (95% CI 0 to 0.13); p= 0.16

Tolerability:
- Teprotumumab: OR 0.8 (95% CI 0.732 to 0.88); p= 0.41
- Tocilizumab: OR 0.44 (95% CI 0.2 to 0.68); p<0.01
- Rituximab: OR 0.54 (95% CI 0.25 to 0.83); p<0.01

CONCLUSIONS

Conclusion: Based on the best available evidence, tocilizumab should be the preferred treatment for moderate to severe GO. In the absence of head-to-head trials, indirect comparisons of treatments are routinely used to estimate the effectiveness of the treatments of interest. In addition, the optimal dose and potential mechanism of action of monoclonal antibodies remain to be established, and it is encouraging that the treatment paradigm for GO may change in the future.

Critique: This analysis is based off of indirect comparisons. Direct comparative trials are needed to further elucidate the comparative safety and efficacy between monoclonal antibodies in the setting of Graves' ophthalmopathy.

Douglas et al., 2022 • Meta-analysis

POPULATION

Objective: To conduct a matching-adjusted indirect comparison of teprotumumab vs intravenous methylprednisolone (IVMP) vs placebo in patients with moderate-to-severe thyroid eye disease

N= 12 studies

METHODS

Literature search parameters: PubMed and Embase were searched for relevant randomized controlled trials (RCTs) and observational studies from database inception to date of search (October 5, 2020) using a search strategy that included key terms and controlled vocabulary (eg, "intravenous steroid," "Graves' orbitopathy," "thyroid eye disease," "Graves' ophthalmopathy"). Results were filtered to include only studies conducted in humans. Regular alerts were established to capture any recent studies until April 1, 2021.

Comparisons: IVMP vs teprotumumab

Outcomes: Changes in proptosis, diplopia response

METHODS

Results (teprotumumab vs IVMP): Change from baseline in proptosis: mean difference (MD) -2.31 mm; 95% CI -3.45 to -1.7

Diplopia response: OR 2.32; 95% CI 1.07 to 5.03

CONCLUSIONS

Conclusion: While this nonrandomized comparison suggests that use of teprotumumab, compared with IVMP, is associated with greater improvements in proptosis and may be twice as likely to have a 1 grade or higher reduction in diplopia, randomized trials comparing these 2 treatments would be warranted to determine if 1 treatment is superior to the other to a clinically relevant degree.

Critique: Results of this analysis are based on indirect comparisons. Direct comparative studies are needed to fully understand the comparative efficacy between IVMP and teprotumumab.

N = 15 RCTs • Li et al., 2022 • Network meta-analysis

POPULATION

Objective: To compare the effects of different treatment modalities on active, moderate-to-severe GO

N= 15 RCTs

METHODS

Literature search parameters: PubMed and Embase were searched for randomized controlled trials published up to November 30, 2020, by using the following search terms: “Graves' orbitopathy”, “thyroid associated orbitopathy”, “thyroid eye disease”, glucocorticoids”, “methylprednisolone”, “orbital radiotherapy”, “mycophenolic acid”, “azathioprine”, “rituximab” and “teprotumumab”. Language restrictions were not imposed in the electronic searches. All relevant trials included in previous systematic reviews and meta-analyses were reviewed.

Comparisons: Placebo vs teprotumumab vs mycophenolate plus intravenous glucocorticoids (IVGCs) vs mycophenolate vs rituximab vs azathioprine vs IVGCs vs orbital radiotherapy (OR) vs oral glucocorticoids (OGCs)

Outcomes: Overall response rate with surface under the cumulative ranking curve (SUCRA), proptosis reduction, change in diplopia grade

METHODS

Results:
Overall response rate:
- No difference between teprotumuab vs mycophenolate + IVGCs, mycophenolate, rituximab, azathioprine, or IVGCs
- Teprotumumab vs OR: risk ratio (RR) 2.75; 95% CI 1.46 to 5.18
- Teprotumumab vs OGC: RR 2.81; 95% CI 1.88 to 8.98

SUCRA rankings: teprotumumab (88.7%), mycophenolate plus IVGCs (74.6%), mycophenolate (72.8%), rituximab (70.8%), azathioprine (47.6%), IVGCs (43.1%), OR (30.1%), OGC (18.8%), placebo (3.4%)

Proptosis reduction:
Teprotumumab vs IVGCs: MD 2.24 (95% CI 0.07 to 4.42); p= 0.043

Changes in diplopia:
No difference between teprotumumab and IVGCs

CONCLUSIONS

Conclusion: Due to the limited number of patients treated with teprotumumab and the lack of comparison with other effective therapeutics, teprotumumab might not become the standard first-line therapy for active, moderate-to-severe GO.

Critique: The heterogeneity among included studies further limits the indirect comparisons included in this analysis

ADVERSE EFFECTS

Dermatological	Alopecia (13%), dry skin (8%)
Gastrointestinal	Nausea (17%), diarrhea (12%)
Integumentary system	Nail disorder (5%)
Metabolic	Hyperglycemia (10%), weight increased (6%), diabetic ketoacidosis (postmarketing), hyperosmolar hyperglycemic state (postmarketing)
Miscellaneous	Fatigue (12%), dysgeusia (8%)
Musculoskeletal	Muscle spasms (25%)

CONTRA-INDICATIONS

None

DRUG INTERACTIONS

No studies evaluating the drug interaction potential have been conducted. Teprotumumab-trbw should not be infused concomitantly with other agents.

STORAGE

Packaged product: Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton until time of use to protect from light. Do not freeze.

Reconstituted product: The combined storage time of reconstituted solution in the vial and the diluted solution in the infusion bag containing 0.9% Sodium Chloride Injection, USP is a total of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) or up to 48 hours under refrigerated conditions 2°C to 8°C (36°F to 46°F) protected from light. Do not freeze the reconstituted or diluted solution.

SAFETY CONSIDERATIONS

BOXED WARNINGS

None

WARNINGS & PRECAUTIONS

- **Infusion Reactions**: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management.
- **Exacerbation of Preexisting Inflammatory Bowel Disease (IBD):** Monitor patients with preexisting IBD for flare of disease; discontinue treatment if IBD worsens.
- **Hyperglycemia**: Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab-trbw).
- **Hearing Impairment Including Hearing Loss**: Teprotumumab-trbw may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with teprotumumab-trbw and consider the benefit-risk of treatment with patients.

IMMUNOGENICITY

In a placebo-controlled study, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with teprotumumab-trbw had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Renal impairment	No clinically significant differences in the pharmacokinetics of teprotumumab-trbw were observed following administration based on mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min.
Hepatic impairment	The effect of hepatic impairment on the pharmacokinetics of teprotumumab-trbw is unknown.
Geriatrics	No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age) in clinical trials.
Pediatrics	Safety and effectiveness have not been established.
Reproductive potential	Advise females of reproductive potential to use effective contraception prior to initiation, during treatment and for 6 months after the last dose.
Pregnancy	Based on findings in animals and its mechanism of action inhibiting IGF-1R, teprotumumab may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies have not been conducted in pregnant women. There are insufficient data in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss. Therefore, teprotumumab-trbw should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose. If the patient becomes pregnant during treatment, teprotumumab-trbw should be discontinued and the patient advised of the potential risk to the fetus.
Lactation	There is no information regarding the presence of teprotumumab-trbw in human milk, the effects on the breast-fed infant or the effects on milk production.

DOSAGE & ADMINISTRATION

Initial: 10 mg/kg

Maintenance: 20 mg/kg every 3 weeks for 7 additional infusions

Standard Concentration: 47.6 mg/mL

Dilution: 0.9% Sodium Chloride Injection, USP

Reconstitution: Sterile Water for Injection, USP

Fluid volume:

- After reconstitution: 10.5 mL
- After dilution (<1,800 mg dose): 100 mL
- After dilution (≥1,800 mg dose): 250 mL

Rate of infusion: Administer the Recombinant Human Hyaluronidase of HYQVIA at an initial rate per site of approximately 1 to 2 mL per minute, or as tolerated. Administer Immune Globulin Infusion 10% (Human) of HYQVIA at rates as shown in the package insert (based on body weight) for the initial infusions. If the patient tolerates these infusions at the full dose and maximum rate, adjust both the time intervals and number of rate changes of the ramp-up used for successive infusions at the discretion of the physician and patient.

Administration

If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion.

Administer the diluted solution intravenously over 90 minutes for the first two infusions. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes.

Do not administer as an intravenous push or bolus. Teprotumumab-trbw should not be infused concomitantly with other agents.

The combined storage time of reconstituted solution in the vial and the diluted solution in the infusion bag is a total of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) or up to 48 hours under refrigerated conditions 2°C to 8°C (36°F to 46°F) protected from light. Do not freeze the reconstituted or diluted solution.

Step 1: Calculate the dose (mg) and determine the number of vials needed for the 10 or 20 mg/kg dosage based on patient weight.

Step 2: Using appropriate aseptic technique, reconstitute each vial with 10 mL of Sterile Water for Injection, USP. Ensure that the stream of diluent is not directed onto the lyophilized powder, which has a cake-like appearance. Do not shake, but gently swirl the solution by rotating the vial until the lyophilized powder is dissolved. The reconstituted solution has a volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg. After reconstitution, the final concentration is 47.6 mg/mL.

Step 3: The reconstituted solution must be further diluted in 0.9% Sodium Chloride Injection, USP prior to infusion. To maintain a constant volume in the infusion bag, a sterile syringe and needle should be used to remove the volume equivalent to the amount of the reconstituted solution to be placed into the infusion bag. Discard the 0.9% Sodium Chloride, USP volume withdrawn.

Step 4: Withdraw the required volume from the reconstituted vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing 0.9% Sodium Chloride Solution, USP to prepare a diluted solution with a total volume of 100 mL (for less than 1,800 mg dose) or 250 mL (for 1,800 mg and greater dose). Mix diluted solution by gentle inversion. Do not shake.

No incompatibilities between teprotumumab-trbw and polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) or polyolefin (PO) bags and intravenous administration sets have been observed.

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