Medical Policy

Subject:	Encapsulated Cell Therapy for Degenerative Ocular Disease		
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Description/Scope

This document addresses therapy using encapsulated cells which are genetically engineered to secrete the protein ciliary neurotrophic factor (CNTF). CNTF has neuroprotective properties on photoreceptors and retinal ganglion cells. The intent of therapy is to slow the progression of retinal degeneration. The encapsulated cell technology is delivered via an intraocular implanted device. The device consists of cells secreting-CNTF in a semipermeable membrane which allows the outflow of therapeutic CNTF while excluding immune system cells.

Position Statement

Medically Necessary:

Ocular encapsulated cell therapy using revakinagene taroretcel-lwey is considered **medically necessary** when the individual has met *all* (A, B, C *and* D) of the following criteria:

A. Adults aged 18 years or older; **and**
B. Diagnosis of macular telangiectasia type 2 in at least one eye with *both* (1 and 2) of the following:
   1. Evidence of fluorescein leakage; **and**
   2. *One or more* of the following features:
      a. Hyperpigmentation outside a 500-micron radius from the center of the fovea; **or**
      b. Retinal opacification; **or**
      c. Crystalline deposits; **or**
      d. Right-angle vessels; **or**
      e. Inner/outer lamellar cavities;
      and
C. Inner segment-outer segment junction line photoreceptor break; **and**
D. Best corrected visual acuity (BCVA) of 54 or greater measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

Investigational and Not Medically Necessary:

Ocular encapsulated cell therapy is considered **investigational and not medically necessary** when the criteria above are not met.

Rationale

On March 6, 2025, The U.S. Food and Drug Administration (FDA) approved Encelto® revakinagene taroretcel-lwey, also known as NT-501 (Neurotech Pharmaceuticals, Inc, Cumberland, RI) for the treatment of idiopathic macular telangiectasia type 2. Encelto is an encapsulated cell therapy delivered via a semipermeable hollow fiber membrane.

The FDA approval is based on the results of 2 unpublished randomized, multi-center, and sham-controlled clinical trials (NCT03316300, NCT03319849). Adults with a diagnosis of idiopathic macular telangiectasia type 2 with photoreceptor inner segment/outer segment (IS/OS) breaks between 0.16 and 2.00 mm² and a BCVA of 54 letters or better. The treatment group receiving intravitreal implants and the sham group undergoing placebo procedures. The primary outcome was the rate of change in the area of EZ loss over 24 months. In both studies, the treatment group reported significantly reduced EZ area loss compared to the sham group (-0.091 mm² in Study 1 [p<0.0001]; -0.049 mm² in Study 2 [p=0.0186]). Secondary outcomes assessed mean changes in retinal sensitivity loss, which varied in significance. Results beyond 24 months were not reported.

In the pivotal studies, 3% of participants tested positive for serum antibodies against recombinant human CNTF (rhCNTF), and another 3% had antibodies against the non-secreted intracellular protein dihydrofolate reductase (DHFR). This may be significant because it raises questions about potential immunogenic responses to Encelto therapy. These antibodies could result in an immune response in affected individuals, potentially affect the safety or efficacy of the therapy. Due to the low reported occurrence, the precise impact remains unknown.

Chew and colleagues (2019) aimed to evaluate the efficacy of a CNTF secreting implant in slowing the progression of macular telangiectasia type 2. The randomized, multi-center sham-controlled clinical trial conducted over 24 months involved 99 eyes from 67 participants aged 21-80. Participants were randomized to receive either treatment via a surgical implant or a sham procedure, with primary outcomes measured using spectral-domain optical OCT imaging. The CNTF-treated group experienced significantly less neurodegeneration compared to the sham group, with a mean difference in photoreceptor loss of 0.05 mm² (p=0.04). While secondary outcomes showed no major differences in visual acuity or reading speed between the groups, retinal sensitivity decline was more pronounced in the sham group (p=0.07). Most adverse ocular events resolved within three months (e.g., conjunctival hemorrhage, ocular pain), though there were some persisting events like delayed dark adaptation (18.8%) and miosis in treated eyes (18.8%). Serious adverse events (SAEs) occurred in 12 participants including death (n=2) occurring in various organ systems. None of the SAEs were attributed to CNTF therapy. The authors concluded that the CNTF secreting device may be a promising treatment for slowing retinal degeneration in macular telangiectasia type 2, warranting further investigation into long-term efficacy and safety.

Chew and associates (2015) reported on the initial safety and tolerability results of intraocular delivery of CNTF using an encapsulated cell implant for treating macular telangiectasia type 2 in an open-label, non-randomized phase I trial with 7 participants. Conducted at two centers, the trial involved placing a high-dose CNTF implant in the worse affected eye of each participant and monitoring them for 36 months. The primary safety outcome was assessed through changes in electroretinogram (ERG). There were no cases of severe ocular inflammation or implant rejection, although transient ERG amplitude reductions were observed in 4 participants at 3 months, which returned to baseline by 12 months. Visual acuity and microperimetry results remained largely unchanged from baseline. Considering these findings, the study concluded that CNTF delivery appears safe and warrants further investigation in randomized controlled trials (RCTs) aimed at evaluating efficacy in slowing disease progression.

Other Neurodegenerative Ocular Disorders

The CNTF implant is being evaluated for other neurodegenerative ocular conditions. These studies are in the early stages of development. While some of these conditions currently have other treatment options available, neuropathic growth factors may represent another treatment option. The current standard treatment of glaucoma involves reducing intraocular pressure (IOP). However, in many affected individuals, disease progression is seen

despite effective IOP reductions (Goldberg, 2023). The effect of a CNTF secreting implant is being assessed for its effect on other optic neuropathies.

Goldberg and associates (2023) published a phase I clinical trial which assessed the safety and efficacy of a high-dose CNTF-secreting NT-501 implant for neuroprotection and neuroenhancement in primary open-angle glaucoma. This open-label, prospective study involved 11 participants who received a high-dose CNTF secreting implant in 1 eye. The untreated eye was used as a control. Over an 18-month period, the study measured AEs, visual acuity, visual field, and retinal nerve fiber layer thickness as outcomes. The results indicated that the CNTF implant was safe and well-tolerated, with no serious AEs reported, and suggested neuroprotective potential with improved stability in visual acuity and contrast sensitivity in the treated eyes, alongside structural improvements in the form of increased retinal nerve fiber layer thickness. The study concluded with plans for a future randomized, phase II trial to further evaluate the implant's efficacy, acknowledging the limitations posed by the trial's small size and open-label design.

Birch and associates (2016) reported on the long-term follow-up results of a multicenter, sham-controlled phase 2 trial involving 36 individuals with retinitis pigmentosa randomly assigned to receive either a high- or low-dose CNTF implant in one eye, with sham surgery in the other. Over the initial 24 months, and optionally extended up to 96 months, eyes retaining the implant experienced a significantly greater visual field loss compared to both explanted and sham eyes, although this difference leveled out after 60 months. No significant long-term benefits were found in terms of visual acuity, visual field sensitivity, or OCT measures of retinal structure across treated and sham groups. The study concluded that while CNTF implants demonstrated biological activity, including increased macular thickness, they did not confer a long-term clinical benefit in visual function.

Background/Overview

Macular telangiectasia type 2 is a bilateral, slowly progressive neurodegenerative retinal condition primarily affecting middle-aged individuals, characterized by the presence of telangiectatic retinal vessels around the macula. In the United States (U.S.) the estimated prevalence is 0.01%. The pathogenesis of the disease is unknown. The disease leads to significant decreases in visual function, manifesting as blurred and distorted vision (metamorphopsia), and central vision loss due to photoreceptor and Müller cell degeneration, though it rarely causes total blindness. The condition results in photoreceptor loss and retinal atrophy, impeding tasks like reading, despite often maintaining distance visual acuity. Macular telangiectasia type 2 can be classified into either nonproliferative (exudative telangiectasia and foveal atrophy) and proliferative (proliferative changes with subretinal neovascularization and fibrosis) disease. Proliferative, also known as neovascular, has been successfully treated with anti-vascular endothelial growth factor (anti-VEGF) drugs (Kedarisetti, 2022). There is currently no proven effective therapy for nonproliferative, also known as non-neovascular, disease.

Hallmarks of macular telangiectasia type 2 include more difficulty with near vision compared to distance vision and central field defects resulting in reduced reading ability. Kedarisetti (2023) notes " For efficient reading, patients need BCVA with preservation of at least four degrees of central field to process words and perform eye movements." While visual acuity is commonly used to assess vision in macular telangiectasia type 2 studies as it correlates with the extent of photoreceptor loss, its effectiveness as a measure can be limited. BCVA often remains stable over long-term follow-ups, even when affected individuals experience significant visual difficulties due to central field defects. In assessing the effectiveness of various treatments for macular telangiectasia type 2, BCVA did not consistently show significant changes, reflecting mixed results regarding its sensitivity as an outcome

measure. Imaging studies, such as fluorescein angiography (FA) and OCT are valuable in diagnosing, monitoring disease as well as providing information regarding retinal thickness and structure. Kedarisetti and associates (2023) recommend a combination of parameters including anatomical assessments, functional sensitivity evaluations, and visual acuity to provide an accurate assessment of treatment efficacy.

Factors associated with macular telangiectasia type 2

Fluorescein leakage, as observed in fluorescein angiography, is a diagnostic feature that can precede visible changes in macular telangiectasia type 2. It is characterized by dilated leaking capillaries, typically temporal to the fovea in the early phase of the angiography. In the late phase, this leakage becomes more diffuse, resulting in hyperfluorescence, which suggests a partial breakdown of the blood-retinal barrier.

The inner segment–outer segment (IS/OS) junction line is a crucial structure in the photoreceptors of the retina. Breaks in this line, as observed in studies using standard OCT, indicate disruptions in the photoreceptors. These breaks can be quantified by measuring the area of the IS/OS line that is disrupted.

An EZ break refers to a disruption or loss of the EZ layer in the retina, which is observable through spectral domain optical coherence tomography (SD-OCT). In the context of macular telangiectasia type 2, the loss of the ellipsoid zone is a significant indicator of disease progression and correlates with functional deterioration of vision. These breaks can lead to noticeable declines in visual acuity, with the loss typically beginning in the area adjacent to the fovea before progressing further.

Proposed treatment

CNTF delivered via encapsulated cell intraocular implants is being evaluated for the treatment of neurodegenerative ocular diseases due to its neuroprotective properties. In preclinical animal studies CNTF has been shown to slow the loss of photoreceptor cells during retinal degeneration by promoting the regeneration of cone outer segments and preventing photoreceptor cell death. CNTF is thought to have the potential to protect photoreceptor cells by downregulating phototransduction and maintaining retinal structure. The use of an intraocular implant is a way to circumvent the blood-retinal barrier. Additionally, the half-life of CNTF is very brief, limiting the possibility of other administrative pathways that delay the delivery of CNTF to the site of action or do not provide constant CNTF delivery.

Definitions

Blood-retinal barrier: Barrier which prevents the penetration of drugs and other agents in the blood into the retina.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

67027	Implantation of intravitreal drug delivery system (eg, ganciclovir implant), includes concomitant removal of vitreous [when specified as intravitreal implantation of Encelto (revakinagene taroretcel-lwey)]

HCPCS

	For the following HCPCS codes when specified as Encelto (revakinagene taroretcel-lwey):
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Diagnosis

H35.071-H35.079	Retinal telangiectasis

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

References

Peer Reviewed Publications:

1. Birch DG, Bennett LD, Duncan JL, et al. Long-term follow-up of patients with retinitis pigmentosa receiving intraocular ciliary neurotrophic factor implants. Am J Ophthalmol. 2016; 170:10-14.
2. Chew EY, Clemons TE, Jaffe GJ, et al; Macular Telangiectasia Type 2-Phase 2 CNTF Research Group. Effect of ciliary neurotrophic factor on retinal neurodegeneration in patients with macular telangiectasia type 2: a randomized clinical trial. Ophthalmology. 2019; 126(4):540-549.
3. Chew EY, Clemons TE, Peto T, et al.; MacTel-CNTF Research Group. Ciliary neurotrophic factor for macular telangiectasia type 2: results from a phase 1 safety trial. Am J Ophthalmol. 2015; 159(4):659-666.e1.
4. Duncan JL. Ciliary Neurotrophic factor treatment improves retinal structure and function in macular telangiectasia type 2. Ophthalmology. 2019; 126(4):550-551.
5. Ghasemi M, Alizadeh E, Saei Arezoumand K, et al. Ciliary neurotrophic factor (CNTF) delivery to retina: an overview of current research advancements. Artif Cells Nanomed Biotechnol. 2018; 46(8):1694-1707.
6. Goldberg JL, Beykin G, Satterfield KR, et al. Phase I NT-501 Ciliary neurotrophic factor implant trial for primary open-angle glaucoma: safety, neuroprotection, and neuroenhancement. Ophthalmol Sci. 2023; 3(3):100298.
7. Kedarisetti KC, Narayanan R, Stewart MW, et al. Macular telangiectasia type 2: a comprehensive review. Clin Ophthalmol. 2022; 16:3297-3309.
8. Runkle AP, Kaiser PK, Srivastava SK, et al. OCT angiography and ellipsoid zone mapping of macular telangiectasia type 2 from the AVATAR study. Invest Ophthalmol Vis Sci. 2017; 58(9):3683-3689.
9. Zhang K, Hopkins JJ, Heier JS, et al. Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration. Proc Natl Acad Sci U S A. 2011; 108(15):6241-6245.
10. Zuzic M, Striebel J, Pawlick JS, et al. Gene-independent therapeutic interventions to maintain and restore light sensitivity in degenerating photoreceptors. Prog Retin Eye Res. 2022; 90:101065.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Encelto™ [Product Information], Cumberland, RI. Neurotech Pharmaceuticals, Inc; Updated March 2025. Available at: https://www.fda.gov/media/185726/download?attachment. Accessed on March 12, 2025.
2. Neurotech Pharmaceuticals. Available at https://clinicaltrials.gov/. Accessed on May 8, 2025.
    - A phase III multicenter randomized, sham controlled, study to determine the safety and efficacy of NT-501 in macular telangiectasia type 2. NCT03316300. Last updated September 24, 2024.
    - A phase III multicenter randomized, sham controlled, study to determine the safety and efficacy of NT-501 in macular telangiectasia type 2. NCT03319849. Last updated September 24, 2024.
    - A phase 2 multicenter randomized clinical trial of ciliary neurotrophic factor (CNTF) for macular telangiectasia type 2 (MacTel). NCT01949324. Last updated September 12, 2018.
    - Extension Study of NT-501 Ciliary Neurotrophic Factor (CNTF) implant for macular telangiectasia (MacTel). NCT03071965. Last updated March 17, 2022.
    - Phase II, multicenter, open-label safety study of bilateral NT-501 in participants with macular telangiectasia type 2. NCT04729972. Last updated March 26, 2025.

Websites for Additional Information

1. American Academy of Ophthalmology (AAO). What Is Macular Telangiectasia? Published September 23, 2024. Available at: https://www.aao.org/eye-health/diseases/macular-telangiectasia. Accessed on May 8, 2025.

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Encelto®
NT-501
revakinagene taroretcel-lwey

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	05/08/2025	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.