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Efgartigimod alfa-fcab or Efgartigimod alfa and hyaluronidase-qvfc

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as

generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) may be self-administered. For self-administered medications, please refer to the applicable pharmacy benefit plan.

Chronic Inflammatory Demyelinating Polyneuropathy

Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) **may be considered medically necessary** to treat individuals 18 years of age or older with chronic inflammatory demyelinating polyneuropathy (CIDP) following previous failure of or contraindication to both immunoglobulin and corticosteroids.

Myasthenia Gravis

Efgartigimod alfa-fcab (Vyvgart®) or efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) **may be considered medically necessary** to treat individuals 18 years of age or older with generalized myasthenia gravis meet ALL the following criteria:

- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification II to IV;
- Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥ 5 ; and
- Inadequate treatment response, intolerance, or contraindication to an acetylcholinesterase inhibitor (e.g., pyridostigmine, neostigmine) and at least ONE immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) either in combination or as monotherapy.

Efgartigimod alfa-fcab (Vyvgart®) or Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) **are considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration (FDA) approved indications, and when the above criteria are not met.

Policy Guidelines

Efgartigimod alfa-fcab

Efgartigimod is supplied in a 400 mg/20 mL single-dose vial. The recommended dose of efgartigimod for adults with gMG is 10 mg/kg given as an IV infusion over 1 hour once weekly for 4 weeks. In individuals weighing ≥ 120 kg, the recommended dose is 1200 mg per infusion. Providers should avoid administration of efgartigimod alfa-fcab to individuals with an active infection. Subsequent treatment cycles should be administered based on clinical evaluation. If a scheduled infusion is missed, the drug may be given up to 3 days after the scheduled time

point. Thereafter, the original dosing schedule can resume until the treatment cycle is completed. Individuals should be monitored during administration and for 1 hour thereafter for clinical signs and symptoms of hypersensitivity reactions. If such a reaction occurs, therapy should be discontinued and appropriate supportive measures instituted. Providers should evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle with efgartigimod alfa-fcab.

Efgartigimod alfa and hyaluronidase-gvfc

Efgartigimod alfa and hyaluronidase-gvfc is supplied as a single-dose vial containing 1008 mg efgartigimod alfa and 11,200 units hyaluronidase per 5.6 mL. Efgartigimod alfa and hyaluronidase-gvfc is intended for subcutaneous administration every 4 weeks by a healthcare professional. Subsequent treatment cycles should be administered based on clinical evaluation. If a scheduled infusion is missed, the drug may be given up to 3 days after the scheduled time point. Thereafter, the original dosing schedule may resume until the treatment cycle is completed. Individuals should be monitored during administration and for 30 minutes thereafter for clinical signs and symptoms of hypersensitivity reactions. If such a reaction occurs, therapy should be discontinued and appropriate supportive measures instituted. Prescribers should evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle with efgartigimod alfa and hyaluronidase-gvfc.

Myasthenia Gravis Foundation of America Clinical Classification

In 1997, the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA) formed a task force to address the need for universally accepted classifications, grading systems, and analytic methods for management of individuals undergoing therapy and for use in therapeutic research trials. As a result, the MGFA Clinical Classification was created. This classification divides myasthenia gravis (MG) into 5 main classes and several subclasses, as follows:

- **Class I:** Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
- **Class II:** Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
 - IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
 - IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- **Class III:** Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
 - IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
 - IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

- **Class IV:** Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
 - IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
 - IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- **Class V:** Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the individual in class IVb.

The Myasthenia Gravis Activities of Daily Living Scale

The Myasthenia Gravis Activities of Daily Living (MG-ADL) scale was developed in the late 1990s to assess the status of symptoms and activities in MG. It is an 8-item, patient reported questionnaire that can be completed in 2–3 minutes with no need for specialized equipment or training. See Table 1.

Table 1. Myasthenia Gravis Activities of Daily Living (MG-ADL) Scale

Grade	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependent
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant

Each activity is scored 0-3; and all scores are totaled to represent the overall MG-ADL score.

Description

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) (also known as chronic inflammatory demyelinating polyradiculoneuropathy) is an acquired, immune mediated neuropathy affecting peripheral nerves and nerve roots, typically characterized by a relapsing remitting or progressive course of symmetric weakness of proximal and distal muscles. CIDP is identified by electrodiagnostic and/or pathologic features of demyelination and responsiveness to immunomodulatory treatments. (3)

Patients with CIDP should have an established diagnosis based on criteria like those established by the American Academy of Neurology in 1991, (4) or those described in guidelines from the European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) guidelines, revised in 2021. The 2021 EAN/PNS guidelines are the 2nd revision of the European Federation of Neurological Societies (EFNS)/PNS guidelines. (5) There is currently no criterion standard set of clinical or electrophysiologic criteria for the diagnosis of CIDP and its variants.

Diagnostic Criteria for CIDP

Table 2. European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) guidelines: Diagnostic Criteria for CIDP (5)

Clinical Criteria for CIDP	
Typical CIDP	CIDP Variants
All of the following: - Progressive or relapsing, symmetric, proximal and distal muscle weakness of upper and lower limbs, and sensory involvement of at least two limbs. - Developing over at least 8 weeks. - Absent or reduced tendon reflexes in all limbs.	One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs): - Distal CIDP: distal sensory loss and muscle weakness predominantly in lower limbs. - Multifocal CIDP: sensory loss and muscle weakness in a multifocal pattern, usually asymmetric, upper limb predominant, in more than one limb. - Focal CIDP: sensory loss and muscle weakness in only one limb. - Motor CIDP: motor symptoms and signs without sensory involvement. - Sensory CIDP: sensory symptoms and signs without motor involvement.
Motor nerve conduction criteria	
1) Strongly supportive of demyelination: <u>At least one of the following:</u>	

- (a) Motor distal latency prolongation $\geq 50\%$ above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
 - (b) Reduction of motor conduction velocity $\geq 30\%$ below LLN in two nerves, or
 - (c) Prolongation of F-wave latency $\geq 20\%$ above ULN in two nerves ($\geq 50\%$ if amplitude of distal negative peak CMAP $< 80\%$ of LLN), or
 - (d) Absence of F-waves in two nerves (if these nerves have distal negative peak CMAP amplitudes $\geq 20\%$ of LLN) + ≥ 1 other demyelinating parameters^a in ≥ 1 other nerve, or
 - (e) Motor conduction block: $\geq 30\%$ reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude $\geq 20\%$ of LLN in two nerves; or in one nerve + ≥ 1 other demyelinating parameters^a except absence of F-waves in ≥ 1 other nerve, or
 - (f) Abnormal temporal dispersion: $> 30\%$ duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) in ≥ 2 nerves, or
 - (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) prolongation in ≥ 1 nerve^b + ≥ 1 other demyelinating parameter^a in ≥ 1 other nerve
- (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms
 - (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms
 - (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms
 - (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms

2) Weakly supportive of demyelination

As in (1) but in only one nerve.

Note 1. These criteria have been established by using a frequency filter bandpass of 2 Hz to 10 kHz for all parameters, except for distal CMAP duration prolongation where separate criteria were defined for four different LFFs of 2, 5, 10, and 20 Hz. Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus.

Note 2. Extensiveness of motor nerve conduction studies (number of nerves to be studied and proximal studies):

- To apply motor nerve conduction criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested.
- If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated at the axilla and at Erb's point.
- Motor conduction block or slowing is not considered in the ulnar nerve across the elbow or the peroneal nerve across the knee.
- Between Erb's point and the wrist, at least 50% CMAP amplitude reduction is required for conduction block in the ulnar and median nerves. Proximal studies of the median nerve may require collision techniques to avoid ulnar nerve components in the median nerve CMAP when recorded from the abductor pollicis brevis muscle (but not when recorded from the flexor carpi radialis muscle).

- For ulnar motor conduction block in the forearm, a Martin-Gruber anastomosis should be ruled out with stimulation of the median nerve at the elbow recording over the abductor digiti minimi muscle.
- For median motor conduction block in the forearm, co-stimulation of the ulnar nerve at the wrist must be ruled out. Stimulation of the median nerve at the wrist while simultaneously recording over the abductor pollicis brevis muscle and the abductor digiti minimi muscle can detect ulnar nerve co-stimulation; stimulation should be adapted so that no CMAP is recorded from the ulnar nerve-innervated abductor digiti minimi muscle.
- If distal CMAP amplitudes are severely reduced (<1 mV), recording from more proximal muscles innervated by the peroneal, median, ulnar or radial nerve may be attempted to demonstrate motor nerve conduction abnormalities meeting electrodiagnostic criteria.

Sensory nerve conduction criteria

1) CIDP

- Sensory conduction abnormalities (prolonged distal latency, or reduced SNAP amplitude, or slowed conduction velocity outside of normal limits) in two nerves.

2) Possible CIDP

- As in (1).
- Sensory CIDP with normal motor nerve conduction studies needs to fulfil a. or b.
 - a) sensory nerve conduction velocity <80% of LLN (for SNAP amplitude >80% of LLN) or <70% of LLN (for SNAP amplitude <80% of LLN) in at least two nerves (median, ulnar, radial, sural nerve), or
 - b) sural sparing pattern (abnormal median or radial sensory nerve action potential [SNAP amplitude] with normal sural nerve SNAP amplitude) (excluding carpal tunnel syndrome).

Note 1. Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus. 1. Since these criteria do not permit to identify normal reference values compatible with sensory nerve demyelination, sensory CIDP cannot be more than a possible diagnosis as based on clinical and electrophysiological criteria.

Note 2. Decline in sural nerve action potential amplitude occurs with age and use of age-dependent reference values after age 60 is advised.

CIDP: chronic inflammatory demyelinating polyneuropathy; LLN: lower limit of normal value; SNAP: sensory nerve action potential; ULN: upper limit of normal value; CMAP: compound muscle action potential; LFF: low frequency filter.

^a Any nerve meeting any of the criteria (a-g).

^b Mitsuma et al.

Myasthenia Gravis

Myasthenia gravis is an acquired, autoimmune disorder that affects the neuromuscular junction of the skeletal muscles. Eighty to 90 percent of individuals with myasthenia gravis have autoantibodies against the acetylcholine receptor (AChR) detectable in serum, and these antibodies are believed to play a central role in disease pathomechanism. The AChR antibodies in myasthenia gravis are primarily immunoglobulin G1 (IgG1) and G3 (IgG3). In addition to blocking ACh binding to the AChR and cross-linking and internalizing the AChRs, these antibodies act through complement activation. (6) Some individuals with myasthenia gravis

who are seronegative for AChR antibodies have antibodies directed against another target on the surface of the muscle membrane, muscle-specific receptor tyrosine kinase. (7) In contrast with AChR antibody-positive myasthenia gravis, in which complement-fixing immunoglobulin G1 (IgG1) and G3 (IgG3) subclasses predominate (8), muscle-specific kinase antibodies are mainly IgG4, (9) the IgG subtype that does not activate complement.

The clinical manifestations can vary from mild and focal weakness in some individuals to severe tetraparesis with respiratory failure in others. Symptom severity may also vary substantially in an individual patient throughout the day and over the course of the condition. Classification systems stratify individuals by symptoms or diagnostic findings to specify the severity of impairment and to aid with management. There are 2 clinical forms - ocular and generalized. In ocular form, weakness is limited to the eyelids and extraocular muscles while in generalized form, weakness involves a variable combination of ocular, bulbar, limb, and respiratory muscles. Myasthenia gravis may be categorized by symptom severity to guide treatment decisions, determine eligibility for clinical trials, and help with prognostication. A widely used classification system from a task force of the Myasthenia Gravis Foundation of America stratifies individuals by the extent and severity of muscle weakness (10) and is summarized in the section of "Policy Guidelines". Myasthenia gravis is a relatively uncommon disorder. Both incidence and prevalence have significant geographical variations. Reported prevalence rates range from 150 to 200 cases per million, and they have steadily increased over the past 50 years, at least partly due to improvements in recognition, diagnosis, treatment, and an overall increase in life expectancy. (11) More recent studies addressing incidence rates have been conducted in Europe and show a wide range from 4.1 to 30 cases per million person-years. (12, 13) The annual rate is lower in studies coming from North America and Japan, with the incidence ranging from 3 to 9.1 cases per million. (14)

The diagnosis is primarily based on clinical testing. Laboratory investigations and procedures can aid the clinician in confirming clinical findings. These may include serologic tests, electrophysiologic exams (e.g., repetitive nerve stimulation test and single-fiber electromyography), an edrophonium test, an ice-pack test, imaging, and laboratory testing for other coexisting autoimmune disorders (e.g., anti-nuclear antibodies, rheumatoid factor, and thyroid function). For most individuals with clinical features of myasthenia gravis, the diagnosis is confirmed by the presence of autoantibodies against the AChRs or against other muscle receptor-associated proteins. A positive anti-AChR antibody is present in 80% of individuals with gMG and confirms the diagnosis in an individual with classical clinical findings. About 5 to 10% of individuals will demonstrate anti-muscle specific kinase antibodies. Individuals who are seronegative for either of these antibodies will have anti-LRP4 antibodies.

Regulatory Status

Efgartigimod alfa-fcab (Vyvgart®) was approved by U.S. Food and Drug Administration (FDA) on December 17, 2021, for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive (anti-AChR-Ab positive). On June 20, 2023, the FDA approved efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) for the same indication. As of May 8, 2026, the FDA expanded the label for both Vyvgart® and Vyvgart

Hytrulo® to include all serotypes of adult patients with generalized myasthenia gravis, including anti-AChR-Ab positive, anti-muscle-specific kinase antibody positive (anti-MuSK-Ab positive), anti-low-density lipoprotein receptor-related protein 4 antibody positive (anti-LRP4-Ab positive), and triple seronegative.

On June 21, 2024, the FDA approved efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP). (2)

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Chronic Inflammatory Demyelinating Polyneuropathy

Efgartigimod alfa and hyaluronidase-qvfc (Vyvgart Hytrulo®) (2)

The efficacy of Vyvgart Hytrulo for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) was established in a two stage, multicenter study (Study 3; NCT04281472). Study 3 included an open-label period to identify Vyvgart Hytrulo responders (stage A) who then entered a randomized, double-blind, placebo-controlled, withdrawal period (stage B). Study 3 enrolled male and female patients aged 18 years and older, who at the time of screening, had a documented diagnosis of definite or probable CIDP using the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS; 2010) criteria for progressing or relapsing forms.

The Inflammatory Neuropathy Cause and Treatment disability score (INCAT) is a scale used to assess the impact of CIDP on daily upper and lower limb function and is composed of the arm score and leg score (0 to 5 points for each). A total score on the INCAT ranges from 0 to 10 points with a higher number representing more disability. The adjusted INCAT (aINCAT) disability score, identical to the INCAT disability score but with changes in the upper limb function from 0 (normal) to 1 (minor symptoms) excluded, was used to assess efficacy for Vyvgart Hytrulo for the treatment of CIDP.

Stage A

In stage A, a total of 322 patients received up to 12 once weekly subcutaneous injections of Vyvgart Hytrulo 1008 mg / 11,200 units until evidence of improvement occurred at two consecutive study visits. Improvement was defined as aINCAT improvement ≥ 1 point, I-RODS improvement ≥ 4 points, or mean grip strength improvement ≥ 8 kPa. Stage A included 228 patients currently receiving standard-of-care therapy and 94 patients who had either not received prior treatment for CIDP or were not treated with standard-of-care therapy for at least 6 months before study entry. Sixty-nine percent of patients (n=221) who had documented improvement at two consecutive visits during Stage A then entered Stage B.

Stage B

In stage B, a total of 221 patients were randomized to receive once weekly subcutaneous injections of Vyvgart Hytrulo 1008 mg / 11,200 units (n=111) or placebo (n=110). Baseline characteristics of patients in stage B were similar between treatment groups. Patients had a median age of 55 years (range: 20 to 82 years), a median time since CIDP diagnosis of 2.2 years, and median INCAT score of 3.0. Sixty-four percent were male and 65% were White, 30% Asian, and 1% African American. Stage B included 146 patients currently receiving standard-of-care therapy and 75 patients who had either not received prior treatment for CIDP or were not treated with standard-of-care therapy for at least 6 months before study entry. The primary endpoint was the time to clinical deterioration defined as a 1-point increase in aINCAT at two consecutive visits or a >1 -point increase in aINCAT at one visit. Patients who had clinical deterioration or completed week 48 in Stage B without clinical deterioration were withdrawn from the placebo-controlled portion of the study. The study stopped when 88 events of clinical deterioration occurred for the primary endpoint analysis. Patients who received Vyvgart Hytrulo experienced a longer time to clinical deterioration (i.e., increase of ≥ 1 point in aINCAT score) compared to patients who received placebo, which was statistically significant, as demonstrated by a hazard ratio of 0.394 [95% confidence interval (0.253; 0.614) $p < 0.0001$].

Myasthenia Gravis

Efgartigimod - Anti-Acetylcholine Receptor Antibody Positive (anti-AChR-Ab positive)

Two formulations are currently approved by the U.S. Food and Drug Administration (FDA) – Vyvgart (efgartigimod alfa-fcab injection for intravenous infusion) and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc for subcutaneous use). The U.S. FDA approval of the intravenous formulation was based on a 26-week, double-blind, placebo-controlled randomized trial called ADAPT, while the approval for the subcutaneous formulation was based on the

results of a bridging 10-week, open-label, randomized trial called ADAPT-SC. These are summarized next.

Randomized Controlled Trials

Trial characteristics and results of the pivotal trials are summarized in Tables 3 and 4, respectively. (1, 15) ADAPT was a double-blind, placebo-controlled, phase 3 trial. While it enrolled individuals regardless of anti-AChR antibody status, the primary endpoint and subsequent approval of efgartigimod by the FDA was only for individuals who were AChR-Ab positive. The study met the primary efficacy endpoint. A statistically significant difference favoring efgartigimod was observed in the Myasthenia Gravis-Activity of Daily Living (MG-ADL) responder rate [67.7% in the efgartigimod -treated group vs 29.7% in the placebo-treated group ($p<.0001$)]. A key secondary endpoint of comparison of the proportion of quantitative myasthenia gravis (QMG) responders between the 2 treatment groups also favored efgartigimod [63.1% in the efgartigimod-treated group vs 14.1% in the placebo-treated group ($p<.0001$)]. The most frequently reported adverse reactions ($\geq 10\%$) were respiratory tract infections, headache, and urinary tract infection.

ADAPT-SC was a randomized open-label parallel-group trial with the objective to demonstrate pharmacodynamic non-inferiority of the subcutaneous formulation to that of the intravenous formulation. (16) It also enrolled individuals regardless of anti-AChR antibody status. The noninferiority evaluation was based on the percent reduction from baseline in AChR-Ab levels at day 29 (i.e., week 4) using a noninferiority margin of 10% meaning that when the lower limit of the 95% confidence interval for the difference is above the margin of -10, the subcutaneous formulation will be considered noninferior to the IV formulation. (17) The least square (LS) mean difference in the percent change from baseline of AChR-Ab levels was 2.5% (95% CI: -7.45 to 2.41), which is below the upper limit of the confidence interval of 10%. (18) Additionally, the 90% CIs for the geometric mean ratios of AChR-Ab reduction at day 29 and AUEC_{0-4w} (area under the effect-time curve from time 0 to 4 weeks post dose) were within the range of 80% to 125%, indicating no clinically significant difference between the two formulations. (2)

Table 3. Summary of Pivotal RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
ADAPT (1) (NCT03669588)	Global	56	Sep 2018- Nov 2019	Inclusion - MGFA clinical classification class II to IV - MG-ADL total score ≥ 5 - On stable dose of myasthenia gravis treatment prior to screening, that included acetylcholinesterase	Efgartigimod 10 mg/kg IV administered as 4 infusions per cycle (1 infusion per week) repeated as needed depending on clinical response no	Placebo given on the same schedule (n=83)

				se inhibitors, steroids, or NSISTs, either in combination or alone • IgG levels ≥ 6 g/L Primary endpoint • Change in proportion of MG-ADL responders from baseline between treatment groups at week 26 in the AChR-Ab positive population^a	sooner than 8 weeks after initiation of the previous cycle for 26 weeks (n=84)	
ADAPT-SC (2) (NCT04735432)	Global	47	Feb 2021-Dec 2021	Inclusion • MGFA clinical classification class II to IV • MG-ADL total score of ≥ 5 with $>50\%$ of the total score attributed to nonocular symptoms. • All individuals received stable doses of their current gMG treatment. Primary endpoint • Percent reduction from baseline in total immunoglobulin G levels at day 29 (that is 7 days after the fourth IV or SC administration)	Efgartigimod alfa 1008 mg/11,200 units of hyaluronidase subcutaneous injection once weekly for 4 weeks (n=55)	Efgartigimod alfa-fcab 10 mg/kg IV administered once weekly for 4 weeks (n=55)

AChR: acetylcholine receptor; gMG: generalized myasthenia gravis; IV: intravenous; MG-ADL: Myasthenia Gravis-Activity of Daily Living; MGFA: Myasthenia Gravis Foundation of America; NSISTs: non-steroidal immunosuppressive therapies; RCT: randomized controlled trial; SC: subcutaneous.

^a MGADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle.

Table 4. Summary of Pivotal RCT Results

Study	Efgartigimod	Placebo
ADAPT (1)		
N	65	67
<i>Primary endpoint</i>		
MG-ADL responders among AChR-Ab positive patients ^a	67.7	29.7
p-value	.0001	
OR (95% CI)	4.95 (2.21 to 11.53)	
<i>Secondary endpoints</i>		
QMG responders among AChR-Ab positive individuals ^b	63.1	14.1
p-value	.0001	
OR (95% CI)	10.84 (4.18 to 31.20)	
ADAPT-SC (2, 18)	Efgartigimod alfa plus hyaluronidase	Efgartigimod alfa
N	44	42
Percent reduction from baseline in AChR-Ab levels at week 4 (day 29) among AChR-Ab positive individuals	62.2%	59.7%
LSM difference	2.5% (95% CI: -7.45 to 2.41)	

Ab: antibody; AChR: acetylcholine receptor; CI: confidence interval; MG-ADL: Myasthenia Gravis-Activity of Daily Living; OR: odds ratio; QMG: Quantitative Myasthenia Gravis; RCT: randomized controlled trial. CI: confidence interval; LSM: least squares mean; MG-ADL: Myasthenia Gravis-Activity of Daily Living; QMG: Quantitative Myasthenia Gravis; RCT: randomized controlled trial.

p-value calculated using mixed effect model for repeated measures.

^a MG-ADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle.

^b QMG responder was defined as a patient who had a 3-point or greater reduction in the total QMG score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after last infusion of the cycle.

The purpose of the study limitations table (Table 5) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following the table and provides the conclusions on the sufficiency of evidence supporting the position statement. The limited representations of African Americans, Asians, and Hispanics makes it challenging to reach conclusions about the efficacy of efgartigimod in these racial groups. Because of the relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of efgartigimod compared with other treatment options. No major limitations in the study design and conduct were identified.

Table 5. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
ADAPT (1)	4. Enrolled populations do not reflect relevant diversity (88% White)				1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; (study duration limited to 26 weeks)

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Efgartigimod - Anti-AChR Antibody Negative (1, 2)

The efficacy of efgartigimod alfa-fcab intravenous (EFG IV) for the treatment of adult patients with gMG who are anti-AChR antibody negative was established in an 8-week, randomized double-blind, placebo-controlled study (Part A; NCT06298552). Patients were treated with EFG IV with the recommended dosage regimen for intravenous administration. Subsequent treatment cycles were administered in the open-label Part B of the study per the recommended dosage regimen for two cycles followed by variable inter-treatment periods no shorter than 7 days for additional cycles for up to two years.

The study enrolled patients with gMG who met the following criteria at screening:

- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV;
- MG-ADL total score of at least 5 ;
- On stable doses of myasthenia gravis therapy prior to screening, that included acetylcholinesterase (AChE) inhibitors, steroids or non-steroidal immunosuppressive therapies (NSISTs), either in combination or alone;
- IgG levels of at least 4 g/L.

In Part A, total of 119 patients were randomized 1:1 to receive once-weekly infusions for 4 weeks of either EFG IV 10 mg/kg (1,200 mg for those weighing 120 kg or more) (n=58) or placebo (n=61).

Baseline characteristics were similar between treatment groups. The median age was 50 years at screening (range: 21 to 80 years; median 49 years for patients treated with EFG IV and 52 years for placebo) and the median time since diagnosis was 4 years. Seventy-six percent of patients were female, and 80% were White, 14% were Asian, and 3% were Black or African American.

At baseline, the median MG-ADL total score was 9 and median QMG total score was 14. At baseline, over 75% of patients in each treatment group received AChE inhibitors and over 60% in each treatment group received steroids at stable doses. There were more patients receiving NSISTs in the EFG IV arm (53%) than those in the placebo arm (36%).

Sixty-one percent (n = 73) of patients were triple seronegative (i.e., anti-AChR, anti-MuSK, and anti-low density lipoprotein receptor-related protein 4 [LRP4] antibodies negative). Thirty-four percent (n = 40) of patients were positive for anti-muscle-specific kinase (anti-MuSK antibodies), and 5% (n = 6) of patients were positive for anti-LRP4 antibodies.

The primary efficacy endpoint was the comparison of the mean change from baseline at Week 4 between treatment groups in the MG-ADL total score. A statistically significant difference favoring EFG IV was observed (LS mean difference [95% CI] = - 1.46 [- 2.50 to -0.41]; p-value = 0.0068).

Practice Guidelines and Position Statements

European Academy of Neurology/Peripheral Nerve Society

A 2021 guideline from the European Academy of Neurology/Peripheral Nerve Society on the diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy offered the following principal treatment recommendation: “intravenous immunoglobulin (IVig) or corticosteroids are strongly recommended as initial treatment in typical CIDP [chronic inflammatory demyelinating polyradiculoneuropathy] and CIDP variants.” (5)

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT04833894 ^a	Evaluating the Pharmacokinetics, Pharmacodynamics, and Safety of Efgartigimod Administered Intravenously in Children with	12	Mar 2027

	Generalized Myasthenia Gravis (ADAPT Jr)		
NCT04980495 ^a	A Phase 3b, Randomized, Open-Label, Parallel-Group Study to Evaluate Different Dosing Regimens of Intravenous Efgartigimod to Maximize and Maintain Clinical Benefit in Patients With Generalized Myasthenia Gravis	69	May 2026
NCT05374590	A Long-term, Single-Arm, Open-label, Multicenter, Follow-on Trial of ARGX-113-2006 to Evaluate Safety of Efgartigimod Administered Intravenously in Children With Generalized Myasthenia Gravis	12	Sep 2028

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J9332, J9334

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. Prescribing Label: Vyvgart® (efgartigimod alfa-fcab) injection, for intravenous use. (May 2026). Available at <<https://www.argenx.com>> (accessed June 8, 2026).
2. Prescribing Label: Vyvgart Hytrulo® (efgartigimod alfa and hyaluronidase-qvfc) injection, for subcutaneous use. (May 2026). Available at <<https://www.argenx.com>> (accessed on June 8, 2026).

Other:

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18. Explore Clinical data for Vygart Hytrulo. Available at <<https://www.vyvgarthcp.com>> (accessed on April 19, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

Policy History/Revision	
Date	Description of Change
07/01/2026	Document updated. The following change was made to Coverage: Removed "Positive serologic test for anti-acetylcholine receptor;" from bulleted criteria for myasthenia gravis. Updated references 1 and 2.
01/01/2026	Document updated. The following changes were made to Coverage: 1) Combined criteria regarding inadequate treatment response under Myasthenia Gravis section with slight modification in language; 2) Removed "Will not receive concurrently with other biologics used to treat myasthenia gravis (e.g., eculizumab, rituximab, immunoglobulin, ravulizumab, rozanolixizumab, or zilucoplan)"; and 3) Added "non-Food and Drug Administration (FDA) approved" to experimental, investigational and/or unproven statement. Added/updated references 1, 2, and 16.
03/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Added conditional coverage for efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) to treat chronic inflammatory demyelinating polyneuropathy; and 2) Modified last three bulleted conditional coverage criteria under the myasthenia gravis section. Added and/or updated all references.
01/01/2024	Document updated with literature review. Coverage revised to add efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) to the medically necessary and experimental, investigational and/or unproven statements. Reference 7 added; others revised. Title changed from Efgartigimod alfa-fcab.
05/01/2022	New medical document. Efgartigimod alfa-fcab (Vyvgart™) may be considered medically necessary for the treatment of generalized myasthenia gravis (MG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive when additional criteria listed in the policy are met. Efgartigimod alfa-fcab (Vyvgart™ is considered experimental, investigational

	and/or unproven for all other indications, and when the above criteria are not met.
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