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| **Policy Effective Date** | **03/15/2025** |
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# Efgartigimod alfa-fcab or Efgartigimod alfa and hyaluronidase-qvfc

| Table of Contents |
|---|
|  |
|  |
|  |
|  |
|  |
|  |
|  |

| Related Policies (if applicable) |
|---|
| RX501.066 Eculizumab |
| RX501.107 Ravulizumab-cwvz |
| |
| |
| |
| |
| |

## Disclaimer

*Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. 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 acceptable standards of medical practice. 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 HCSC 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 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 (MG) meet ALL the following criteria:

- Positive serologic test for anti-acetylcholine receptor;
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification II to IV;
- Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥5;
- Inadequate treatment response, intolerance, or contraindication to an acetylcholinesterase inhibitor (e.g., pyridostigmine, neostigmine);
- Inadequate treatment response or intolerance to at least ONE immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) or contraindication to all;
- Will not receive concurrently with other biologics used to treat myasthenia gravis (e.g., eculizumab, rituximab, immunoglobulin, ravulizumab, rozanolixizumab, or zilucoplan).

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

## Policy Guidelines

**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–specific Activities of Daily Living scale (MG-ADL)**

The Myasthenia Gravis–specific Activities of Daily Living scale (MG-ADL) was developed in the late 1990s to assess the status of symptoms and activities in MG.11 It is an 8-item, patient reported questionnaire that can be completed in 2–3 minutes with no need for specialized equipment or training. (1) See Table 1.

**Table 1. MG Activities of Daily Living (MG-ADL) Profile**

| **Grade** | **0** | **1** | **2** | **3** | **Score (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 users 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 | |

Myasthenia Gravis–specific Activities of Daily Living scale: MG-ADL

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. (2)

Patients with CIDP should have an established diagnosis based on criteria like those established by the American Academy of Neurology in 1991, (3) 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. (4) There is currently no criterion standard set of clinical or electrophysiologic criteria for the diagnosis of CIDP and its variants.

<u>Diagnostic Criteria for CIDP</u>

**Table 2. European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) guidelines: Diagnostic Criteria for CIDP (4)**

<table>
<tr><th colspan="2">Clinical Criteria for CIDP</th></tr>
<tr><th>Typical CIDP</th><th>CIDP Variants</th></tr>
<tr><td>All of the following:<ul><li>Progressive or relapsing, symmetric, proximal and distal muscle weakness of upper and lower limbs, and sensory involvement of at least two limbs.</li><li>Developing over at least 8 weeks.</li><li>Absent or reduced tendon reflexes in all limbs.</li></ul></td><td>One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs):<ul><li>Distal CIDP: distal sensory loss and muscle weakness predominantly in lower limbs.</li><li>Multifocal CIDP: sensory loss and muscle weakness in a multifocal pattern, usually asymmetric, upper limb predominant, in more than one limb.</li><li>Focal CIDP: sensory loss and muscle weakness in only one limb.</li><li>Motor CIDP: motor symptoms and signs without sensory involvement.</li><li>Sensory CIDP: sensory symptoms and signs without motor involvement.</li></ul></td></tr>
<tr><td colspan="2">Motor nerve conduction criteria</td></tr>
<tr><td colspan="2">1) Strongly supportive of demyelination:<br><u>At least one of the following:</u><br>(a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or<br>(b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or<br>(c) Prolongation of F-wave latency ≥20% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN), or<br>(d) Absence of F-waves in two nerves (if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN) + ≥1 other demyelinating parameters[a] in ≥1 other nerve, or<br>(e) Motor conduction block: ≥30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥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<br>(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<br>(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<ul><li>(LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms</li><li>(LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms</li><li>(LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms</li><li>(LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms</li></ul>(2) Weakly supportive of demyelination</td></tr>
</table>

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. (5) 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. (6) In contrast with AChR antibody-positive myasthenia gravis, in which complement-fixing immunoglobulin G1 (IgG1) and G3 (IgG3) subclasses predominate (7), muscle-specific kinase antibodies are mainly IgG4 (8) 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 from, 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 (9) 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. (10) 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. (11, 12) 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. (13)

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. On June 20, 2023, the FDA approved efgartigimod alfa and hyaluronidase-qvfc (Vyvgart® Hytrulo) for the same indication.

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). (14)

## 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) (14)

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% CI (0.253; 0.614) p<0.0001].

Section Summary: Chronic Inflammatory Demyelinating Polyneuropathy

For individuals with CIDP who receive efgartigimod alfa and hyaluronidase-gvfc (Vyvgart® Hytrulo), the evidence includes a multicenter study with an open-label period to identify responders who then entered a randomized, double-blind, placebo-controlled, second stage. Participants included patients aged 18 years and older with a documented diagnosis of definite or probably CIDP. The primary endpoint was the time to clinical deterioration defined as a 1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment disability score (aINCAT) at two consecutive visits or a >1-point increase in aINCAT at one visit. 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Myasthenia Gravis**

Efgartigimod

Two formulations are currently approved by the U.S. Food and Drug Administration (FDA) – Vygart (efgartigimod alfa-fcab injection for intravenous infusion) and Vygart 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. (15, 16) 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 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 (≥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. 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 $AUEC_{0\text{-}4w}$ (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. (14)

**Table 3. Summary of Pivotal RCT Characteristics**

| Study | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | **Active** | **Comparator** |
| ADAPT (15) (NCT03669588) | Global | 56 | Sep 2018-Nov 2019 | Inclusion<br>• MGFA clinical classification class II to IV<br>• MG-ADL total score ≥5<br>• On stable dose of myasthenia gravis treatment prior to screening, that included acetylcholinesterase inhibitors, steroids, or NSISTs, either in combination or alone<br>• IgG levels ≥6 g/L<br><br>Primary endpoint<br>• Change in proportion of MG-ADL responders from baseline between treatment groups at week 26 in the AChR-Ab positive population[a] | Efgartigimod 10 mg/kg IV administered as 4 infusions per cycle (1 infusion per week) repeated as needed depending on clinical response no sooner than 8 weeks after initiation of the previous cycle for 26 weeks (n=84) | Placebo given on the same schedule (n=83) |

| | | | | | | |
|---|---|---|---|---|---|---|
| ADAPT-SC (14) (NCT04735432) | Global | 47 | Feb 2021-Dec 2021 | Inclusion<br>• MGFA clinical classification class II to IV<br>• MG-ADL total score of ≥5 with >50% of the total score attributed to nonocular symptoms.<br>• All individuals received stable doses of their current gMG treatment.<br>Primary endpoint<br>• Percent reduction from baseline in total immuno-globulin G levels at day 29 (that is 7 days after the fourth IV or SC administra-tion) | 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 (15)** | | |
| N | 65 | 67 |
| *Primary endpoint* | | |
| 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) | |
| *Secondary endpoints* | | |
| 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 (14, 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 (15) | 4. Enrolled populations do not reflect relevant diversity (88% White) | | | | 1. Not sufficient duration for benefit;<br>2. Not sufficient duration for harms;<br>(study duration limited to 26 weeks) |

The study limitations stated in this table are those notable in the current literature 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.

Section Summary: Myasthenia Gravis

Two formulations are currently approved by the FDA: Vygart (efgartigimod alfa-fcab injection for intravenous infusion) and Vygart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc for subcutaneous use). Initial FDA approval of the intravenous formulation was based on a single RCT called ADAPT. Results of this trial reported a statistically significant difference in the primary endpoint favoring efgartigimod in MG-ADL responder rate compared with the placebo (67.7% vs 29.7%, respectively; p<.0001). A key secondary endpoint of responder based on QMG total score at week 26 also favored efgartigimod compared with placebo (63.1% vs 14.1%, respectively; p<.0001). The most frequently reported adverse reactions (≥10%) were respiratory tract infections, headache, and urinary tract infection. Subsequent approval of the subcutaneous formulation was based on the results of a bridging 10-week open-label randomized trial called ADAPT-SC. Results of this trial demonstrated pharmacodynamic non-inferiority based on the percent reduction in AChR-Ab levels from baseline to day 29. The LS mean difference was 2.5% (95% CI: -7.45 to 2.41), which was below the upper limit of the confidence interval of 10%. The limited representations of African Americans, Asians, and Hispanics in the ADAPT trial make 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.

**Practice Guidelines and Position Statements**

There are no practice guidelines or position statements identified that would likely influence this medical policy.

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 6.

**Table 6. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|

| | | | |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT04833894[a] | Evaluating the Pharmacokinetics, Pharmacodynamics, and Safety of Efgartigimod Administered Intravenously in Children with Generalized Myasthenia Gravis (ADAPT Jr) | 12 | Mar 2027 |
| NCT04818671[a] | Evaluating the Long-Term Safety and Tolerability of Efgartigimod PH20 SC Administered Subcutaneously in Patients with Generalized Myasthenia Gravis (ADAPTSC+) | 184 | Dec 2024 |
| 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 |
| ***Unpublished*** | | | |
| NCT04735432 (ADAPTsc) | Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 SC Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis (ADAPTsc) | 11 | Nov 2023 |

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®) ©2023 American Medical Association: Chicago, IL.

## References


1. Muppidi S, Wolfe GI, Conaway M, et al. MG-ADL: still a relevant outcome measure. Muscle Nerve. Nov 2011; 44(5):727-731. PMID 22006686
2. Lewis RA and Muley SA. Chronic inflammatory demyelinating polyneuropathy: Etiology, clinical features, and diagnosis. In: UpToDate, Shefner J (Ed), Waltham, MA. Available at <https://www.uptodate.com> (accessed September 20, 2024).
3. Research Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Neurology. May 1991; 41(5):617-618. PMID 2027473
4. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society Guideline on Diagnosis and Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Report of a Joint Task Force - second revision. J Peripher Nerv Syst. Sep 2021; 26(3)242-268. PMID 34085743
5. Punga AR, Maddison P, Heckmann JM, et al. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. Lancet Neurol. Feb 2022; 21(2):176-188. PMID 35065040
6. Vincent A, McConville J, Farrugia ME, et al. Antibodies in myasthenia gravis and related disorders. Ann N Y Acad Sci. Sep 2003; 998:324-335. PMID 14592891
7. Rødgaard A, Nielsen FC, Djurup R, et al. Acetylcholine receptor antibody in myasthenia gravis: predominance of IgG subclasses 1 and 3. Clin Exp Immunol. Jan 1987; 67(1):82-88. PMID 3621677
8. McConville J, Farrugia ME, Beeson D, et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. Ann Neurol. Apr 2004; 55(4):580-584. PMID 15048899
9. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. Jul 12 2000; 55(1):16-23. PMID 10891897
10. Phillips LH. The epidemiology of myasthenia gravis. Ann N Y Acad Sci. Sep 2003; 998:407-412. PMID 14592908
11. Somnier FE, Engel PJ. The occurrence of anti-titin antibodies and thymomas: a population survey of MG 1970-1999. Neurology. Jul 09 2002; 59(1):92-98. PMID 12105313
12. MacDonald BK, Cockerell OC, Sander JW, et al. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain. Apr 2000; 123 (Pt 4):665-676. PMID 10733998

13. McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. Neuroepidemiology. 2010; 34(3):171-183. PMID 20130418
14. U.S. Food and Drug Administration. Drugs@FDA. Highlights of Prescribing Information. Vyvgart® Hytrulo. (June 2024). Available at <https://www.accessdata.fda.gov> (accessed September 20, 2024).
15. Prescribing Label: Vyvgart (efgartigimod alfa-fcab) injection, for intravenous use. Available at <https://www.argenx.com> (accessed on September 20, 2024).
16. Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. Jul 2021; 20(7):526-536. PMID 34146511
17. Statistical Analysis Plan for NCT04735432. Posted August 16, 2022. Available at <https://classic.clinicaltrials.gov> (accessed on April 19, 2024).
18. Explore Clinical data for Vygart Hytrulo. Available at <https://www.vyvgarthcp.com> (accessed on April 19, 2024).

## 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 |
|---|---|
| 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. |