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Effective Date: 08/08/2024

Efgartigimod Products
Vyvgart® (efgartigimod alfa-fcab)
Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc)

HCPCS: Vyvgart: J9332; Vyvgart Hytrulo: J9334

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

- A. Coverage of the requested drug is provided when all the following are met:
- a. FDA approved indication
 - b. FDA approved age
 - c. Diagnosis of myasthenia gravis
 - i. Documented anti-acetylcholine receptor (AChR) antibody positive myasthenia gravis (MG) identified by:
 1. Lab record or chart notes identifying the patient is positive for anti-AChR antibodies AND
 2. One of the following confirmatory tests:
 - a) Positive edrophonium test
 - b) History of clinical response to oral cholinesterase inhibitors (for example: pyridostigmine)
 - c) Electrophysiological evidence of abnormal neuromuscular transmission by repetitive nerve stimulation (RNS) or single-fiber electromyography (SFEMG)
 - ii. Patients must NOT have a history of:
 1. Thymectomy within 3 months
 2. Current thymoma
 3. Other neoplasms of the thymus
 - iii. Previous treatment courses of at least 12 weeks with one of the following standards of care have been ineffective: methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, or tacrolimus unless all are contraindicated or not tolerated
 - iv. Patient is currently receiving, and will continue to receive, a stable standard of care regimen
 - v. Must not be used with other biologic therapies or immunoglobulin therapy for myasthenia gravis
 - d. Diagnosis of chronic idiopathic demyelinating polyneuropathy (CIDP) (Vyvgart Hytrulo Only)
 - i. Significant functional disability
 - ii. Definitive diagnosis based on the electrodiagnostic criterion from the Joint Task Force of the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS)

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- iii. If probable CIDP based on the electrodiagnostic criteria from the Joint Task Force of the EFNS/PNS, then documentation of elevated spinal fluid protein on lumbar puncture or an MRI showing enlarged or enhancing nerves confirming the diagnosis
- iv. Trial and failure, contraindication, or intolerance to generic corticosteroids or immunoglobulin therapy
- v. Must not be used in combination with other biologic therapies or immunoglobulin therapy for CIDP
- e. Trial and failure, intolerance, or a contraindication to the preferred products as specified in the BCBSM/BCN medical utilization management drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria

- a. Quantity Limits: Align with FDA recommended dosing
- b. Authorization Period: One year at a time
- c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Vyvgart is a neonatal Fc receptor blocker indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
- Vyvgart Hytrulo is a combination of efgartigimod alfa, a neonatal Fc receptor blocker, and hyaluronidase, an endoglycosidase, indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and chronic inflammatory demyelinating polyneuropathy (CIDP).
- Myasthenia Gravis
 - Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular, or class I, MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Depending on the severity of muscle weakness, at this point MG is classified as either class II for mild, class III for moderate, and class IV for severe presentation. Those with class V disease require intubation due to profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Vyvgart and Vyvgart Hytrulo have only been studied in patients with class II – IV disease. There is no safety and efficacy data to support use of either drug in patients with class I or V disease at this time.
 - Vyvgart and Vyvgart Hytrulo are only indicated for use in patients with anti-AChR antibodies. An immunologic assay to detect for the presence of anti-AChR antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has anti-AChR antibodies, at least one other confirmatory test including a positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) should be conducted.

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- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2021 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Vyvgart has not been studied in patients who have undergone thymectomy within 3 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Vyvgart or Vyvgart Hytrulo in these patient populations at this time.
- Safety and efficacy of Vyvgart were established in the ADAPT trial, a randomized, double-blind, placebo-controlled, phase 3 trial of 167 patients with generalized myasthenia gravis regardless of anti-acetylcholine receptor antibody status. Patients had class II – IV disease and were already stable on at least one treatment, which included acetylcholinesterase inhibitors, corticosteroids, or immunosuppressants, for MG prior to study entry. They also had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 indicated they had greater than 50% of symptoms that were non-ocular. Patients were randomly assigned to 10 mg/kg efgartigimod or placebo administered as four infusions per cycle with one infusion given per week repeated as needed depending on clinical response no sooner than 8 weeks after initiation of the previous cycle. The primary endpoint was proportion of acetylcholine receptor antibody-positive patients who were MG-ADL responders defined as a greater than or equal to 2-point MG-ADL improvement sustained for greater than or equal to 4 weeks in the first treatment cycle. The trial met its primary endpoint with 67.7% of efgartigimod-treated acetylcholine receptor-antibody positive gMG patients being responders on the MG-ADL score compared to 29.7% of placebo patients which was statistically significant (p-value < 0.0001).
- Safety and efficacy of Vyvgart Hytrulo were established in the ADAPT-SC trial, a randomized, open-label, parallel-group, phase 3 trial of 110 patients with generalized myasthenia gravis regardless of anti-acetylcholine receptor antibody status. Patients had class II – IV disease and were already stable on at least one treatment, which included acetylcholinesterase inhibitors, corticosteroids, or immunosuppressants, for MG prior to study entry. Patients were randomly assigned to 10 mg/kg Vyvgart or 1,008 mg/11,200 units Vyvgart Hytrulo. The primary endpoint was noninferiority of Vyvgart Hytrulo to Vyvgart. Noninferiority was met (p-value < 0.0001) and Vyvgart Hytrulo demonstrated a mean total IgG reduction of 66.4% from baseline at day 29 compared to 62.2% with Vyvgart. Additional key secondary endpoints were met, which were consistent with efficacy measures from the ADAPT study identifying the correlation between total IgG reduction and clinical benefit in gMG.
- Standard therapies recommended by the 2021 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, rituximab, Soliris®, IVIG, and PLEX.
 - Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.
 - Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect doses should be maintained for six months to two years of therapy and then tapered to the lowest effective dose.
- Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents that are better supported by randomized clinical trial data.
- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.
- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX. Patients were excluded from the ADAPT trial if they had received IVIG or undergone PLEX 1 month prior to the start of the study.
- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. Treatment guidelines state rituximab should be considered as an early therapeutic option in patients with MuSK antibody positive MG who have an unsatisfactory response to initial immunotherapy. The efficacy of rituximab in refractory AChR antibody positive MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive agents. Patients were excluded from the ADAPT trial if they had used rituximab 6 months prior to the start of Vyvgart therapy.
- Soliris should be considered in the treatment of severe, refractory, AChR antibody positive generalized MG. Until further data become available to allow comparisons of cost and efficacy with other treatments guidelines state, Soliris should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. Patients were excluded from the ADAPT trial if they had received Soliris 6 months prior to the start of Vyvgart therapy.
- Vyvgart and Vyvgart Hytrulo have not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Soliris.
- Chronic Inflammatory Demyelinating Polyneuropathy
 - CIDP is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots. It is characterized by a relapsing-remitting or progressive course, glucocorticoid responsiveness, and electrodiagnostic or pathologic features of demyelination. In its classic form, CIDP manifests as a symmetric, motor-predominant neuropathy that results in both proximal and distal muscle weakness.

Recognized variants include asymmetric and/or sensory-predominant forms. All share the common pathophysiology of inflammatory demyelination. Although relatively rare, CIDP is important to recognize among the varied causes of polyneuropathy as it is treatable with immunomodulatory therapies.

- There is a temporal continuum between acute inflammatory demyelinating polyneuropathy (AIDP), which is the demyelinating form of Guillain-Barré syndrome (GBS), and CIDP. The time course of progression and the occurrence of relapses are used to distinguish between these entities. GBS commonly reaches its nadir within three to four weeks but does not progress beyond eight weeks. CIDP continues to progress or has relapses for greater than eight weeks. GBS is typically monophasic, but up to two relapses in the first eight weeks from onset can occur. Three or more relapses in the first eight weeks is highly suggestive of acute CIDP. Relapses closer to the eight week time period is more suggestive of CIDP.
- The diagnosis of CIDP should be considered in patients presenting with a progressive or relapsing-remitting polyneuropathy involving both motor and sensory axons along with areflexia, particularly when weakness predominates and affects proximal and distal muscles simultaneously and symmetrically. While the initial suspicion for CIDP is clinical, the diagnosis is confirmed by evidence of peripheral nerve demyelination, which must be demonstrated by electrodiagnostic findings or rarely by nerve biopsy, and exclusion of other disorders that may cause or mimic CIDP.
 - Electromyography (EMG) should be performed in all patients with suspected CIDP and is a critical component of the evaluation. The characteristic electrophysiologic features of a definitive CIDP diagnosis per the EFNS/PNS guidelines are those of peripheral nerve demyelination which include at least one of the following:
 - Greater than or equal to 50% prolongation of motor distal latency above the upper limit of normal in two nerves
 - Greater than or equal to 30% reduction of motor conduction velocity below the lower limit of normal in two nerves
 - Greater than or equal to 20% prolongation of F-wave latency above the upper limit of normal in two nerves or greater than 50% if the amplitude of the distal negative peak compound motor action potential (CMAP) is less than 80% of the lower limit of normal
 - Absence of F waves in two nerves, if these nerves have amplitudes of distal negative peak CMAPs greater than or equal to 20% of the lower limit of normal, plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve
 - Partial motor conduction block, defined by a greater than 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal, in two nerves, or in one nerve plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve
 - Abnormal temporal dispersion, defined by a greater than 30% duration increase between the proximal and distal negative peak CMAP in at least two nerves
 - Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in at least one nerve (median greater than or

equal to 6.6 ms, ulnar greater than or equal to 6.7 ms, peroneal greater than or equal to 7.6 ms, tibial greater than or equal to 8.8 ms) plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- The EFNS/PNS guidelines state probable CIDP is considered when patients have greater than or equal to 30% amplitude reduction of the proximal negative peak CMAP relative to the distal, excluding the posterior tibial nerve, if the distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal in two nerves or in one nerve plus at least one other demyelinating parameter meeting any of the definite criteria in at least one other nerve.
- Cerebrospinal fluid (CSF) analysis is recommended in patients with probable CIDP and particularly for patients in whom the clinical and electrophysiologic findings are inconclusive. Albuminocytologic dissociation is a hallmark of CIDP and represents supportive evidence in the EFNS/PNS diagnostic criteria for probable CIDP.
- Magnetic resonance imaging (MRI) with gadolinium of the spine (including spinal roots, cauda equina), brachial plexus, lumbosacral plexus, and other nerve regions can be used to look for enlarged or enhancing nerves. MRI abnormalities are useful as supportive criteria for probable CIDP in the EFNS/PNS guideline.
- Early administration of effective treatment is important in CIDP. The goal is to stop the immune attack against the myelin sheath of peripheral nerves so that secondary axonal degeneration is minimized. This can improve symptoms and function and can prevent or minimize long-term disability. The treatment approach depends on the severity and course of disease. While some patients with CIDP have such mild disease with minimal impact on function and quality of life that treatment is not required, most patients are significantly impaired and need treatment. Multiple medication trials may be required to optimize treatment response, particularly for patients with severe disease. Serial clinical examinations are used to monitor for relapses and guide changes in therapy. Once symptoms stabilize, and for patients who present with milder symptoms, the treatment objective is for sustained improvement and to promote remission.
- For most treatment-naïve patients with CIDP who are more than mildly affected or for mildly affected patients who are rapidly worsening, the European Academy of Neurology and Peripheral Nerve Society recommend initial immune-modulatory treatment using either intravenous immune globulin (IVIG), plasma exchange, or glucocorticoids. The initial choice among these therapies is influenced by disease severity, concurrent illness, venous access, treatment side effects, availability, and cost.
- Vyvgart Hytrulo has not been studied and there is no data to support use in combination with other medications used to treat CIDP, such as, immunoglobulin.

References:

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Policy History		
#	Date	Change Description
1.7	Effective Date: 08/08/2024	Updated to include the new indication of chronic idiopathic demyelinating polyneuropathy for Vyvgart Hytrulo
1.6	Effective Date: 08/10/2023	Updated to include Vyvgart Hytrulo. Name of the policy was changed from Vyvgart to Efgartigimod Products due to the addition of a second product to the policy
1.5	Effective Date: 07/13/2023	UM medical management system update for BCBS and BCN for Vyvgart Hytrulo
1.4	Effective Date: 07/10/2023	UM medical management system update for MAPPO and BCNA for Vyvgart Hytrulo
1.3	Effective Date: 02/02/2023	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 03/01/2022	UM medical management system update for MAPPO and BCNA for Vyvgart
1.1	Effective Date: 02/10/2022	New Policy
1.0	Effective Date: 01/13/2022	UM medical management system update for BCBS and BCN for Vyvgart

* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.