Drug Monograph

Drug Name: **Vyvgart™ (efgartigimod alfa) vial**
Drug Class: **Central Nervous System: Myasthenia Gravis Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Vyvgart is available in a 400 mg/20 mL single-dose vial.
Manufacturer:	Distributed by: Argenx US, Inc., Boston, MA 02110.
Summary of Findings:	Vyvgart was evaluated in the Phase 3 ADAPT trial, a 26-week randomized, double-blind, placebo-controlled study. Participants were randomly assigned (1:1) to Vyvgart (10 mg/kg) or matching placebo, administered as 4 infusions per cycle (1 infusion per week). The efficacy of Vyvgart was measured using the MG-ADL score, which assesses the impact of . generalized myasthenia gravis (gMG) on daily functions of 8 signs or symptoms that are typically affected in gMG. A statistically significant difference favoring Vyvgart was observed in the Myasthenia Gravis Activities of Daily Living (MG-ADL) responder rate during the first treatment cycle (67.7% in the Vyvgart-treated group vs. 29.7% in the placebo treated group; *P <0.0001*). The efficacy of Vyvgart was also measured using QMG as a secondary endpoint. During the first treatment cycle, 63.1% of patients in the Vyvgart-treated group were considered QMG responders vs. 14.1% in the placebo group (*P <0.0001*).
Status Recommendation:	☐ Clinical Edit ☒ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular condition that causes muscle weakness. The muscle weakness can occur in different areas of the body, but most commonly occurs in the eye, face, neck, and limb muscles. Generalized myasthenia gravis (gMG) is a more severe form of MG that involves muscle groups besides just the eye muscles. MG can be broken down into five classes characterized by the amount of muscle weakness along with the affected areas of the body.

Myasthenia Gravis Foundation of America Clinical Classification	
Class	**Description**
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.
Class III	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
Class IV	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
Class V	Intubation, with or without mechanical ventilation (excludes intubation used during routine postoperative management).

Classes II-IV can be further divided into categories a or b depending on if the muscle weakness predominately affects the limbs and axial muscles or the oropharyngeal, respiratory muscles, respectively.

About 80% of all MG cases are caused by autoantibodies targeting acetylcholine receptors (AChR) involved with nerve-muscle communication. The remaining cases target other neuromuscular transmitters such as muscle-specific kinase (Mu-SK) and lipoprotein-related protein 4 (LPRP4). Those with MG tend to have an enlarged thymus gland that does not shrink as normally seen from childhood to adulthood. It is hypothesized that this abnormal thymus contributes to the development of this autoimmune disease. MG is considered a rare neurological disease with worldwide prevalence ranging from 150 to 200 cases per million. In North America, incidence of MG is estimated at 3 to 9.1 cases per million. MG is evenly distributed between men and women, but onset of symptoms/disease varies between male and female. Women tend to get diagnosed younger, before the age of 40 years old most often. While many men with MG, are diagnosed before the age of 65 years old.

Dosage Form [3]

Vyvgart is available in a 400 mg/20 mL single-dose vial.

Manufacturer [3]

Distributed by: Argenx US, Inc., Boston, MA 02110.

Indication(s) [3]

Vyvgart is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Vyvgart is a human IgG1 antibody fragment that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG.

Pharmacokinetics:

Absorption	N/A
Metabolism	Degrades by proteolytic enzymes into small peptides and amino acids
Excretion	Renal: <1% recovered in the urine
Half-life	80-120 hours

Clinical Trials Experience

STUDY DESIGN (NCT03669588)	Phase 3, 26-week, randomized, double-blind, placebo-controlled ADAPT study (N=167)
INCLUSION CRITERIA	• Male or female patients aged ≥ 18 years. • Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) class II, III, IVa and IVb.

EXCLUSION CRITERIA	• Pregnant and lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing.
	• Male patients who are sexually active and do not intend to use effective methods of contraception during the trial or within 90 days after the last dosing or male patients who plan to donate sperm during the trial or within 90 days after the last dosing.
	• MGFA Class I and V patients.
	• Patients with worsening muscle weakness secondary to concurrent infections or medications.
	• Patients with known seropositivity or who test positive for an active viral infection at Screening with:
	  ○ Hepatitis B Virus (HBV) (except patients who are seropositive because of HBV vaccination)
	  ○ Hepatitis C Virus (HCV)
	  ○ Human Immunodeficiency Virus (HIV)

TREATMENT REGIMEN	Participants were randomly assigned (1:1) to Vyvgart (10 mg/kg) or matching placebo, 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.

<table>
<tr><td>RESULTS</td><td>The primary endpoint was proportion of AChR-Ab–positive patients who were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks) in the first treatment cycle. A statistically significant difference favoring VYVGART was observed in the MG-ADL responder rate during the first treatment cycle [67.7% in the VYVGART-treated group vs 29.7% in the placebo-treated group (p <0.0001)].
The secondary endpoint was a comparison of the percentage of QMG responders during the first treatment cycle between both treatment groups in the AChR-Ab–positive patients.

<table>
<tr><th></th><th>Vyvgart N=65 %</th><th>Placebo N=64 %</th><th>P-value</th><th>Odds Ratio (95% CI)</th></tr>
<tr><td>MG-ADL Responders</td><td>67.7</td><td>29.7</td><td><0.0001</td><td>4.951 (2.213, 11.528)</td></tr>
<tr><td>QMG Responders</td><td>63.1</td><td>14.1</td><td><0.0001</td><td>10.842 (4.179, 31.200)</td></tr>
</table>
Abbreviations: MG-ADL=Myasthenia Gravis Activities of Daily Living QMG =Quantitative Myasthenia Gravis; mITT=modified intent-to treat; n=number of patients for whom the observation was reported; CI = confidence interval; Logistic regression stratified for AChR-Ab status (if applicable), Japanese/Non-Japanese and standard of care, with baseline MG-ADL as covariate / QMG as covariates Two-sided exact p-value</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Contraindications (3,4)

- None

Warnings and Precautions (3,4)

- Infections: Delay administration of Vyvgart to patients with an active infection. Monitor for signs and symptoms of infection in patients treated with Vyvgart. If serious infection occurs, administer appropriate treatment, and consider withholding Vyvgart until the infection has resolved.
- Hypersensitivity Reactions: Angioedema, dyspnea, and rash have occurred. If a hypersensitivity reaction occurs, discontinue the infusion and institute appropriate therapy.

Adverse Effects (3,4)

Most common, ≥5%	Vyvgart (N=84) %	Placebo (N=83) %
Respiratory tract infection	33	29
Headache[1]	32	29
Urinary tract infection	10	5
Paraesthesia[2]	7	5
Myalgia	6	1

[1] Headache includes migraine and procedural headache.
[2] Paresthesia includes oral hypoesthesia, hypoesthesia, and hyperesthesia.

Drug Interactions (3,4)

- Concomitant use of Vyvgart with medications that bind to the human neonatal Fc receptor (FcRn) (e.g., immunoglobulin products, monoclonal antibodies, or antibody

derivates containing the human Fc domain of the IgG subclass) may lower systemic exposures and reduce effectiveness of such medications. Closely monitor for reduced effectiveness of medications that bind to the human neonatal Fc receptor. When concomitant long-term used of such medications is essential for patient care, consider discontinuing Vyvgart and using alternative therapies.

Dosage and Administration [3,4]

- The recommended dosage of Vyvgart is 10 mg/kg administered as an intravenous (IV) infusion over one hour once weekly for 4 weeks. In patients weighing 120 kg or more, the recommended dose of Vyvgart in 1200 mg (3 vials) per infusion.
- Vyvgart should be administered via IV infusion by a healthcare professional. It must be diluted prior to administration.
- Administer subsequent treatment cycles based on clinical evaluation. The safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.
- If a scheduled infusion is missed, Vyvgart may be administered up to 3 days after the scheduled time point. Thereafter, resume the original dosing schedule until the treatment cycle is completed.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Efgartigimod alfa-fcab	Vyvgart™	Argenx US, Inc.	10 mg/kg IV infusion over one hour once weekly for 4 hours; for patients >120kg the dose is 1200 mg per infusion	$5,950/20 mL

** Wholesale Acquisition Cost

Conclusion

Vyvgart is a first-in-class human immunoglobulin G1 (IgG1) antibody fragment that binds the neonatal Fc receptor (FcRn), keeping antibodies in circulation and preventing FcRn from recycling IgG back into the blood. This causes a reduction in overall levels of IgG, including the abnormal AChR antibodies that are present in most patients with gMG. Vyvgart was evaluated in the Phase 3 ADAPT trial, a 26-week randomized, double-blind, placebo-controlled study. Participants were randomly assigned (1:1) to Vyvgart (10 mg/kg) or matching placebo, administered as 4 infusions per cycle (1 infusion per week). The efficacy of Vyvgart was measured using the MG-ADL score, which assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG. A statistically significant difference favoring Vyvgart was observed in the MG-ADL responder rate during the first treatment cycle (67.7% in the Vyvgart-treated group vs. 29.7% in the placebotreated group; *P <0.0001*). The efficacy of Vyvgart was also measured using QMG as a secondary endpoint. During the first treatment cycle, 63.1% of patients in the Vyvgart-treated group were considered QMG responders vs. 14.1% in the placebo group (*P <0.0001*). The most common AEs were respiratory tract infections, headache, and urinary tract infections. Over the next 2 years, additional pipeline agents are likely to be approved for gMG, potentially allowing payers to manage this therapeutic area more aggressively.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) National Institute of Neurological Disorders and Stroke. (2020).*Myasthenia Gravis Fact Sheet*. Nih.gov. Published March 2020. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet. Date accessed 01/05/2022.
2) Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. *JClinMed*, 2021;*10*(11), 2235. https://doi.org/10.3390/jcm10112235
3) Vyvgart (efgartigimod alfa-fcab) [package insert]. Argenx: FDA package insert; 2021
4) IPD Analytics: New Drug Review: Vyvgart (efgartigimod alfa-fcab). Accessed February 14, 2022.
5) U.S. National Library of Medicine. An Efficacy and Safety Study of ARGX-113 in Patients with Myasthenia Gravis Who Have Generalized Muscle Weakness (ADAPT). https://clinicaltrials.gov/ct2/show/NCT03669588?term=NCT03669588&draw=2&rank=1. Accessed February 14, 2022.

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