

# New Drug Fact Blast

## Clinical Services

<b>Drug/Manufacturer:</b>	<b>Vyvgart™ (efgartigimod alfa-fcab) [argenx]</b>														
<b>Dosage Formulations:</b>	Solution for injection: 400 mg/20 mL (single dose vial)														
<b>FDA Approval Date:</b> <b>FDB File Date:</b>	FDA: December 17, 2021 FDB: December 26, 2021														
<b>Indication:</b>	Neonatal Fc receptor (FcRn) blocker for the treatment of generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody positive.														
<b>Mechanism of Action:</b>	Vyvgart is a human Immunoglobulin G1 (IgG1) antibody fragment that binds to the neonatal Fc receptor. The neonatal Fc receptor is responsible for protecting IgG from breakdown and therefore, extending its half-life and keeping it in circulation longer. Because Vyvgart competes with IgG for the receptor site, it results in the reduction of circulation of IgG. Less IgG implies that there will be less breakdown of acetylcholine within the neuromuscular junctions, leading patients to experience less symptoms and muscles weakness.														
<b>Dose/ Administration:</b>	<p>Vyvgart is administered as a one-hour long intravenous infusion in treatment cycles. It can only be administered by a trained healthcare professional within a doctor's office or at an infusion center.</p> <p>For adults weighing less than 120kg:</p> <ul style="list-style-type: none"> <li>Administer 10mg/kg IV infusion once weekly for 4 weeks.</li> </ul> <p>For adults weighing more than 120kg:</p> <ul style="list-style-type: none"> <li>Administer 1,200 mg IV infusion once weekly for 4 weeks</li> </ul> <p>Administration of subsequent treatment cycles is based on clinical evaluation. Time between treatment cycles should be no sooner than 50 days (7.14 weeks). The average time between treatment cycles during clinical trials was approximately 10 weeks.</p> <p>If a scheduled infusion is missed, may administer the infusion up to 3 days after the scheduled time point. Thereafter, resume the original dosing schedule until the treatment cycle is completed.</p>														
<b>Disease State Clinical Highlights:</b>	<ul style="list-style-type: none"> <li>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.</li> <li>MG can be broken down into five classes characterized by the amount of muscle weakness along with the affected areas of the body.</li> </ul> <table border="1"> <thead> <tr> <th colspan="2">Myasthenia Gravis Foundation of America Clinical Classification</th> </tr> <tr> <th>Class</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td>Class I</td> <td>Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.</td> </tr> <tr> <td>Class II</td> <td>Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.</td> </tr> <tr> <td>Class III</td> <td>Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.</td> </tr> <tr> <td>Class IV</td> <td>Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.</td> </tr> <tr> <td>Class V</td> <td>Intubation, with or without mechanical ventilation (excludes intubation used during routine postoperative management).</td> </tr> </tbody> </table>	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).
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).														

	<ul style="list-style-type: none"> <li>○ 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.</li> <li>• 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).</li> <li>• 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.</li> <li>• 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.</li> <li>• 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 the majority of men with MG, are diagnosed before the age of 65 years old.</li> </ul>
<b>Drug Clinical Highlights:</b>	<ul style="list-style-type: none"> <li>• Vyvgart is an IgG1 antibody fragment that acts as a FcRn antagonist. FcRn is responsible for recycling IgG for continued circulation. By blocking this receptor site, the amount of IgG1 within the body will decrease and lessen the autoimmune response. It is the only FcRn antagonist that is a human antibody fragment. It is also the first product that the pharmaceutical company, argenx, has brought to market.</li> </ul> <p><u>Contraindications:</u> None</p> <p><u>Warnings and Precautions</u></p> <ul style="list-style-type: none"> <li>• Infections: Delay administration if an active infection is present. Monitor for signs and symptoms of an infection during treatment course. If a serious infection occurs during a Vyvgart treatment cycle, consider stopping Vyvgart and treating the infection until resolution.</li> <li>• Hypersensitivity Reactions: Reactions such as, angioedema, dyspnea, and rash have occurred. If a hypersensitivity reaction does occur, discontinue the infusion, and implement appropriate therapy.</li> <li>• Immunizations: Because Vyvgart causes a transient reduction in IgG levels, immunization with live-attenuated or live vaccines is not recommended during treatment with Vyvgart. Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle with Vyvgart.</li> </ul> <p><u>Pregnancy/Lactation</u></p> <ul style="list-style-type: none"> <li>• Maternal use at the recommended clinical dose of Vyvgart is expected to reduce maternal IgG antibody levels and may result in measurable fetal exposure because antibodies are transported across the placenta during pregnancy. In animal reproductive studies, no effects of embryo-fetal development were observed in pregnant rats or in pregnant rabbits treated with Vyvgart at doses three to ten times the recommended human dose.</li> <li>• There is no information regarding the presence of Vyvgart in human milk or its effect on lactation.</li> </ul> <p><u>Pediatrics</u></p> <ul style="list-style-type: none"> <li>• The safety and efficacy of Vyvgart has not been established in participants less than 18 years old.</li> </ul> <p><u>Drug Interactions</u></p> <ul style="list-style-type: none"> <li>• Medications that bind to FcRn (e.g., contain the human Fc domain for IgG, like immunoglobulin products or monoclonal antibodies) may lower systemic exposure and reduce effectiveness of both Vyvgart and other medications that bind to FcRn.</li> </ul>

### Clinical Studies

- ADAPT trial (n = 167) (NCT03669588): randomized, double-blind, placebo-controlled, Phase III, 26-week efficacy and safety study. Participants were randomized to the placebo group (n = 83) or the intervention group (n = 84). Participants who weighed less than 120kg received Vyvgart dosing at 10mg/kg per infusion. Participants who weighed over 120kg received 1200mg of Vyvgart. The trial participants were administered four infusions per cycle (one infusion per week), repeated as needed depending on clinical response but no sooner than 8 weeks after initiation of the previous cycle.
  - Key Inclusion Criteria:
    - Male or female patient aged greater than or equal to 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
    - MG-Activities of Daily Living (MG-ADL) total score of  $\geq 5$ 
      - Used as patient tool to determine symptom severity
      - Score out of a possible 24 points
      - Higher score indicates more severe symptoms
    - On stable dose of MG therapy prior to screening, including acetylcholinesterase (AChE) inhibitors, steroids, or non-steroidal immunosuppressive therapies (NSISTs), either in combination or alone
    - IgG levels of at least 6 g/L (Normal range for adults is 6 to 16 g/L)
  - Key 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)
  - Primary Outcome Measure: Efficacy compared to placebo based on the percentage of "Myasthenia Gravis Activities of Daily Living (MG-ADL) responders" in the acetylcholine receptor-antibody (Ab) seropositive population. A MG-ADL responder was defined as a 2 point or greater improvement in participant's MG-ADL score that was sustained for 4 weeks or more.
  - Primary Secondary Measure: Efficacy compared to placebo based on the percentage of Quantitative Myasthenia Gravis (QMG) responders during the first treatment cycle in the AChR-Ab positive participants. A QMG responder was defined as 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.
    - Used as a clinical research tool for more objective determination of patient symptom severity.
    - Score is out of 39 possible points.
    - Higher scores indicate more severe symptoms.

### MG-ADL Responders During Cycle 1 in AChR-Ab Positive Patients

	Vyvgart n=65 %	Placebo n=64 %	P-value	Odds Ratio (95% CI)
MG-ADL Responders	67.7	29.7	< 0.0001	4.951 (2.213, 11.528)
QMG Responders	63.1	14.1	< 0.0001	10.842 (4.179, 31.200)

- Adverse reactions: (reported in ≥ 5% and more frequently than placebo)
  - 3 patients from the treatment group and 3 patients from the placebo group discontinued treatment during the study.

	Vyvgart n=65 %	Placebo n=64 %
Respiratory tract infection	33	29
Headache <sup>1</sup>	32	29
Urinary tract infection	10	5
Paraesthesia <sup>1</sup>	7	5
Myalgia	6	1

<sup>1</sup>Headache includes migraine and procedural headache.

<sup>2</sup>Paraesthesia includes oral hypoesthesia, hypoesthesia, and hyperesthesia.

- Immunogenicity (defined as the detection of anti-efgartigimod alfa-fcab antibodies in the clinical trials)
  - 20% (17/83) of participants developed antibodies
  - 7% (6/83) of participants developed neutralizing antibodies

#### Price Per Unit (WAC):

- \$5,950.00 per 20 mL vial
- The estimated annualized cost per 70 kg patient
  - 70 kg-patient x 10 mg/kg = 700 mg per infusion = \$11,900 per infusion (2 vials)
  - Regimen is four infusions per cycle = \$47,600 per treatment cycle
  - Assuming 1 cycle every 8 weeks (6 cycles per year) = \$285,600 per year or
  - Assuming 1 cycle every 10 weeks (5 cycles per year) = \$238,000 per year
- However, based on approved Vyvgart dosing the annual cost could potentially range greatly:
  - \$47,600 - \$428,400 per year
  - This range takes into consideration a 70 kg patient needing only one treatment cycle within a year to a patient over 120 kg getting treatment cycles throughout the entire year.

#### Therapeutic Alternatives:

- There is no cure for MG, but according to the Neurology Clinics journal there are four types of therapies for symptom management that are mainstays for the treatment of gMG.
  - One of the first-line therapies for symptomatic MG is acetylcholinesterase inhibitors (e.g., oral pyridostigmine) to prevent the breakdown of acetylcholine and increase the amount within the neuromuscular junction. It is first line because it has limited risk of neurotoxicity, as it does not cross the blood-brain barrier, and it can be used long term without diminishing effectiveness over time.
  - Second line therapy is chronic immunosuppressive therapy to try and repress the immune system dysregulation. The most common types of immunotherapy used for gMG are glucocorticoids or nonsteroidal immunosuppressants. This is generally used adjunct with acetylcholinesterase inhibitors for additional symptom control or for more severe MG. Typically, the more severe MG cases need higher steroid dosing. Nonsteroidal immunosuppressants are often added to the treatment regimen to reduce the steroid usage.

- The third type of treatment is rapid immunomodulatory therapies, including IVIG and plasma exchange that are generally reserved for either severe MG or for patients experiencing a myasthenia crisis.
- The last type of treatment is thymectomy, which was previously reserved for patients with a thymoma, but is now finding more utilization in younger patients who are seropositive for anti-acetylcholine antibodies. Currently, only about 10 to 20% of patients with MG have thymomas, and about 80% of MG patients are anti-AChR seropositive.
- Based on the clinical trials, Vyvgart's place in therapy will be for patients who are refractory to traditional immunosuppressive treatment options. There are other therapeutic alternatives that have a similar place in therapy, and other FcRn antagonists that are in the pipeline.
- Soliris has a similar FDA-approved indication and place in therapy as Vyvgart. Soliris has a higher annual cost compared to Vyvgart, but current clinical trials suggest that Soliris has a longer, more consistent symptom control.

Medication	Cost (WAC)/ Year	Route of Administration	Mechanism of Action	Indication
Pyridostigmine	\$2,500	Oral	Acetylcholinesterase inhibitor	First-line therapy for treatment of MG
Prednisone	< \$500	Oral	Immunosuppressive	Adjunct therapy for additional symptom control for MG
Azathioprine	\$5,800	Oral	Non-steroidal Immunosuppressive	Second-line therapy for MG patients on steroids that need additional symptom control
Vyvgart	\$250,000	IV infusion	FcRn antagonist	Treatment of gMG in AChR-Ab positive patients
Chronic IVIG	\$14,000 - \$49,000 per course	IV infusion	Immunomodulatory	Off-label for refractory gMG or myasthenia crisis in seropositive or seronegative patients
Rituximab	\$1,300,000	IV infusion	B-cell suppression	Off-label for gMG; effective as early therapy for MuSK-positive patients
Soliris	\$600,000	IV infusion	Complement inhibitor	FDA-approved for refractory gMG in AChR-Ab positive patients

WAC = Wholesale acquisition cost

**Prior Authorization Approval Criteria:**

**Must meet the following criteria:**

Initial Therapy:

- Participant has documented diagnosis of generalized myasthenia gravis **AND**
- Documented positive anti-acetylcholine receptor (AChR) antibody test **AND**
- Myasthenia Gravis Foundation of America (MGFA) Class II, III, or IV **AND**
- Documented baseline Myasthenia Gravis Activities of Daily Living (MG-ADL) score of greater than or equal to 6 **OR**



- Documented baseline Quantitative Myasthenia Gravis (QMG) score of greater than or equal to 12 **AND**
- Prescribed by or in consultation with neurologist, rheumatologist, or other specialist in the treated disease state **AND**
- Participant aged 18 years or older **AND**
- Participant is not currently pregnant **AND**
- Adequate therapeutic trial of 2 immunosuppressants (90/120 days) **AND**
- Dose does not exceed 1200 mg per infusion **AND**
- No more than 24 infusions per year
- Initial approval period: 3 months

Continuation of Therapy:

- Subsequent cycles to be administered if:
  - The MG-ADL score is greater than or equal to 6 **OR**
  - The QMG score is still greater than or equal to 12 **OR**
  - If the patient was an MG-ADL/ QMG responder initially, but no longer has a clinically meaningful improvement (defined as < 2-point improvement in total MG-ADL score or defined as < 3-point improvement in total QMG score) **AND**
- Treatment has a sustained effect for at least 4 weeks after the end of the previous treatment cycle **AND**
- Participant has continued non-pregnant status **AND**
- Minimum time between treatment cycles should be no less than 50 days from the start of previous treatment cycle and the start of the next treatment cycle
- Continuation approval period: 6 months

**Implication to State Medicaid Program:**

- LOE: 2035
- Argenx has reached agreements with several payers to create value-based agreements. Details of these contracts are currently not public.
- Due to Vyvgart's lower cost and potential for fewer infusions, it will likely be required that MG patients need to step through Vyvgart before trying Soliris.
- Ongoing clinical trials:
  - Phase III trials for chronic inflammatory demyelinating polyradiculoneuropathy; Idiopathic thrombocytopenic purpura; Pemphigus
  - Phase II trials for bullous pemphigoid
- Pipeline Therapies:

Trial Description	Estimated Primary Completion	NCT
Phase III follow-on trial of the Vyvgart ADAPT study. Patients with generalized myasthenia gravis to receive efgartigimod/ hyaluronidase by SC administration or efgartigimod by IV infusion to compare.	2023	NCT04735432
Phase III trial of the complement inhibitor, Ultomiris, in adult patients with generalized myasthenia gravis. Predicted to replace Soliris as same mechanism of action, but dosing schedule for Ultomiris is every 8 weeks instead of every 2 weeks.	2022	NCT03920293
Phase III trial of the FcRn antagonist, rozanolixizumab, in adult patients with generalized myasthenia gravis.	2023	NCT03971422
Phase III trial of the complement inhibitor, Zilucoplan, in adult patients with generalized myasthenia gravis.	2023-2024	NCT03315130

**References:**

- Vyvgart (efgartigimod alfa-fcab) [package insert]. Argenx: FDA package insert; 2021
- Vyvgart Drug Monograph. Clinical Pharmacology. <https://www.clinicalkey.com/pharmacology/monograph/5373?n=VYVGART>. Date accessed 01/03/2022.
- 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.
- IPD Analytics: New Drug Review: Vyvgart (efgartigimod alfa-fcab). Date accessed 01/06/2022.
- Dresser L, Wlodarski R, Reznia K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. *JClinMed*, 2021; 10(11), 2235. <https://doi.org/10.3390/jcm10112235>
- Farmakidis C, Pasnoor M, Dimachkie M, Barohn RJ. Treatment of Myasthenia Gravis. *NeuroClin*, 2018;36(2);311–337. <https://doi.org/10.1016/j.ncl.2018.01.011>
- Lascano AM, Lalive PH. Update in immunosuppressive therapy of myasthenia gravis. *AutoimmunRev*, 2021;20(1);102712. <https://doi.org/10.1016/j.autrev.2020.102712>

DRAFT