Efgartigimod alfa-fcab (VYVGART)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

Efgartigimod alfa-fcab is human IgG1 antibody Fc fragment engineered to reduce pathogenic IgG autoantibody levels.

Indication(s) Under Review in This Document

- Treatment of generalized myasthenia gravis in adults who are antiacetylcholine receptor (AchR)antibody positive

Dosage Form(s) Under Review

- 10 mg/kg IV once weekly for 4 weeks with a maximum dose of 1.2 grams IV. Subsequent treatment cycles may be administered based on clinical evaluation and no sooner than 50 days from the start of the previous treatment cycle.

Clinical Evidence Summary

The pivotal approval trial was the ADAPT study, a 26-week multinational, randomized, double-blind, placebo-controlled phase III trial[2]. Patients with generalized myasthenia gravis who had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5 (> 50% non-ocular) and were receiving stable doses of ≥ 1 myasthenia gravis treatment (e.g., acetylcholinesterase inhibitors (AChE), corticosteroids and/or nonsteroidal immunosuppressive therapy [NSISTs]) were randomized to receive intravenous efgartigimod 10 mg/kg (n = 84) or placebo (n = 83) administered as weekly infusions over four weeks per cycle.

A total of 167 patients were enrolled in Study 1 and were randomized to receive either efgartigimod alfa-fcab 10mg/kg (1200 mg for those weighing 120 kg or more) (n=84) or placebo (n=83). Baseline characteristics were similar between treatment groups. Patients had a median age of 46 years at screening (range: 19 to 81 years) and a median time since diagnosis of 9 years. Seventy-one percent were female, and 84% were White. Median MG-ADL total score was 9, and median Quantitative Myasthenia Gravis (QMG) total score was 16. The majority of patients (n=65 for efgartigimod alfa-fcab; n=64 for placebo) were positive for AChR antibodies.

At baseline, over 80% of patients in each group received AChE inhibitors, over 70% in each treatment group received steroids, and approximately 60% in each treatment group received NSISTs, at stable doses.

The primary efficacy endpoint was the comparison of the percentage of Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) responders during the first treatment cycle between treatment groups in the AChR-Ab positive population. A statistically significant difference favoring efgartigimod alfa-fcab was observed in the MG-ADL responder rate during the first treatment cycle [67.7% in the efgartigimod alfa-fcab -treated group vs 29.7% in the placebo-treated group ($p < 0.0001$)]. The secondary endpoint was the comparison of the percentage of Quantitative Myasthenia Gravis (QMG) total score responders during the first treatment cycle between both treatment groups in the AChR-Ab positive patients. A statistically significant difference favoring efgartigimod alfa-fcab was observed in the QMG responder rate during the first treatment cycle [63.1% in the efgartigimod alfa-fcab -treated group vs 14.1% in the placebo-treated group ($p < 0.0001$)].

Predefined exploratory analyses did not show any efficacy differences based on gender, age, or baseline MG-ADL (data not shown). Concomitant use of NSISTs also did not affect efficacy, with 18 (72%) MG-ADL responders of the 25 acetylcholine receptor antibody-positive patients in the efgartigimod group who were not on NSISTs. Of the 45 acetylcholine receptor antibody-positive efgartigimod-treated patients with previous thymectomy, 27 (60%) were MG-ADL responders, compared with 17 (85%) of 20 patients who had not previously undergone thymectomy. In patients who received a second cycle, a greater proportion of patients in the efgartigimod group (36 [71%] of 51) were MG-ADL responders compared with the placebo group (11 [26%] of 43), with similar rates to cycle 1.

Safety Considerations

Other warnings / precautions:

- Infections: Delay administration of efgartigimod to patients with an active infection. Monitor patients for signs and symptoms of infection. If serious infection occurs, administer appropriate treatment and consider withholding 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 reactions**
  - **Common**: common adverse events occurring in ≥ 10% of efgartigimod recipients (n = 84) and at a higher incidence than in placebo recipients (n = 83) included headache (29% vs 28%), upper respiratory tract infection (11% vs 5%) and urinary tract infection (10% vs 5%). Most of reported infections were mild to moderate in severity.
  - **Serious Adverse events / Deaths / Discontinuation: Four** (5%) efgartigimod treated patients developed one of each of thrombocytosis, rectal adenocarcinoma, myasthenia gravis worsening (each leading to treatment discontinuation), and depression. In the placebo group, seven (8%) patients had a serious adverse event,

including one case each of myocardial ischemia, atrial fibrillation, and spinal ligament ossification, which all led to treatment discontinuation. The remaining events were upper respiratory infection, spinal compression fracture, myasthenia gravis worsening, and myasthenia gravis crisis.

- The rate of infections is important, as patients with myasthenia gravis are predisposed to infections, probably exacerbated by concomitant immunosuppressive treatments. In the efgartigimod-treated group, 46% of patients had an infection compared with 37% in the placebo group. Most infections were mild to moderate, with only two graded as severe in the efgartigimod-treated patients.

Other Therapeutic Options[3,4]

Alternative treatments for myasthenia gravis are listed in table 3 below. Additionally, first line chronic immunotherapies are in Table 4.

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Efgartigimod	TBD	Well-tolerated. Allergic reactions, headache, infections, leukopenia, myalgia Effective in generalized MG patients who remain highly symptomatic after treatment with pyridostigmine, steroids or NSI	Weak recommendation for patients still symptomatic on pyridostigmine, steroids or NSIST. Only approved for AChR Ab + MG, but may work for other MG Subtypes.
Eculizumab	NF, CFU	Treatment refractory, highly symptomatic AChR Ab+ MG Effective in refractory AChR Ab+ generalized MG, with long term steroid-sparing effects	Well-tolerated. Infusion-related reactions, severe meningococcal infection, other infections, headaches, musculoskeletal pain
Ravulizumab	TBD		

Table 4 Chronic Immunotherapies [4]

Drug	Formulary status	Time to onset of effect	Time to maximal effect	Position
Azathioprine	F	12 months	1-2 years	MG not controlled with low steroid dose
Cyclosporine	F	6 months	7 months	Limited role due to toxicity
Mycophenolate mofetil	F	6-12 months	1-2 years	MG not controlled with low steroid dose
Prednisone	F	2-3 weeks	5-6 months	Ocular and generalized MG who do not respond to pyridostigmine (level B). Monotherapy in selected patients if they are controlled by a low dose
Tacrolimus	F	6 months	12 months	MG not controlled with low steroid dose

Projected Place in Therapy

- The ADAPT study used four validated myasthenia gravis-specific outcome measures, utilizing both patient-reported and physician-reported information, to assess the effects of efgartigimod in patients with generalized myasthenia gravis. Notably, the primary and some secondary endpoints required patients to have a clinically meaningful improvement in the associated outcome measure, and for this improvement to persist for at least 4 weeks.
- The ADAPT trial showed that efgartigimod was well tolerated and efficacious in patients with generalized myasthenia gravis. The reduction in disease burden and improvement in strength and quality of life in patients with generalized myasthenia gravis were consistent across four myasthenia gravis-specific scales, and these benefits were observed early and were reproducible and durable.
- Existing therapies including corticosteroids and NSISTs, broadly suppress the immune system and do not selectively target IgG autoantibodies that are central to generalized myasthenia gravis pathophysiology. These therapies are usually accompanied by side-effects such as glucose intolerance, weight gain, arterial hypertension, osteoporosis, gastrointestinal issues, bradycardia, and renal dysfunction.
- Efgartigimod may provide a therapy which can be considered steroid sparing and provide additional benefit when added to other NSIST agents. It provides a rapid onset (in ADAPT, patients saw results as early as 2 weeks).
- Patients in the ADAPT trial and receiving other immunotherapies realized additional benefit with the addition of efgartigimod.

References

[1] Vyvgart™ [prescribing information]. Boston, MA: Argenx US, Inc.; December 2021.

[2] Howard JF, Jr, 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. 2021;20(7):526–536.

[3] Menon D, Bril V. Pharmacotherapy of Generallized Myasthenia Gravis with Special Emphasis on Newer Biologicals. Drugs 2022

[4] Alhaidar M, et al. Current Treatment of Myasthenia Gravis. J Clin Med 2022, 11, 1597

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