Nipocalimab-aahu (IMAAVY) in Generalized Myasthenia Gravis
National Drug Mini-monograph
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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Nipocalimab-aahu is a recombinant human IgG1λ monoclonal antibody that functions as a neonatal Fc receptor (FcRn) blocker. It binds to FcRn, preventing the receptor from recycling endogenous IgG and thereby leading to a reduction in circulating IgG levels.
Indication Under Review[1]	Treatment of generalized myasthenia gravis (gMG) in adult and pediatric patients 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive
Dosage Regimen	Initial Dose: Single dose of 30mg/kg IV administered over at least 30 minutes Maintenance Dose: 15mg/kg IV administered over at least 15 minutes every 2 weeks (starting 2 weeks after initial dose) Must be diluted with 0.9% sodium chloride Must use 0.2 micron in-line or add on filter
Dosage Forms Under Review	300 mg/1.62 mL (185 mg/mL) 1,200 mg/6.5 mL (185 mg/mL)

EFFICACY CONSIDERATIONS

Trial	**Vivacity-MG**	**Vivacity-MG3**
Design	A phase 2 multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. The study included a 4-week screening period, an 8-week double-blind treatment period, and an 8-week follow-up. Patients were randomized 1:1:1:1:1 to placebo or one of four nipocalimab dosing regimens. Acetylcholinesterase inhibitors were held 10 hours before efficacy assessments.	A phase 3, multicenter, randomized, double-blind, placebo-controlled study. Randomization was 1:1 and stratified by antibody status, baseline MG-ADL score (≤9 or >9), and region. The double-blind phase lasted 24 weeks. An open-label extension is ongoing.
Population	N=68. Adults with gMG with a positive serologic test for anti-AChR or anti-MuSK autoantibodies who had an inadequate response to stable standard-of-care (SOC) therapy. Insufficient symptom control was defined as a Quantitative Myasthenia Gravis (QMG) score of ≥12 and an MG-ADL score of ≥4, despite being on stable SOC therapy. Patients were required to be MGFA Clinical Classification Class II-IVa. Key exclusion criteria were any concurrent biologic drug therapy, rituximab or eculizumab within 12 months, IVIg or plasmapheresis within 6 months, unresected thymoma, or thymectomy within 12 months. Of note, there were 4 (6%) participants who were MuSK+.	N=153. Adults with gMG (MGFA Class II-IV) who were inadequately controlled with SOC therapy, defined as an MG-ADL score ≥6. Patients were required to be on stable doses of SOC therapy. Key exclusion criteria were any concurrent biologic drug therapy for MG, rituximab or eculizumab within 6 months, IVIg or plasmapheresis within 6 weeks, unresected thymoma, or thymectomy within 12 months. Of note, there were 16 (10%) participants who were MuSK+, and 3 (2%) participants who were LRP4+. Most (>50%) were MGFA class I-II. The primary efficacy analysis was performed on the intent-to-treat population of antibody-positive patients (AChR+, MuSK+, or LRP4+).
Intervention	Four different IV nipocalimab dosing regimens were tested in addition to SOC therapy: 5 mg/kg Q4W, 30 mg/kg Q4W, 60 mg/kg Q2W, or a single 60 mg/kg dose	Nipocalimab administered as a 30 mg/kg loading dose, followed by a maintenance dose of 15 mg/kg every two weeks, added to SOC therapy.
Comparator	IV placebo Q2W, added to SOC therapy	IV placebo Q2W, added to SOC therapy
Results	A statistically significant dose-response trend was observed for the change from baseline in MG-ADL score at day 57 (p=0.03) Nipocalimab treatment resulted in rapid, substantial, and dose-dependent reductions in total serum IgG levels, with a maximal reduction of 83% in the 60 mg/kg Q2W group. Magnitude of IgG lowering had a positive correlation with magnitude of anti-AChR autoantibody lowering and improved (lower) MG-ADL score.	Primary endpoint: The least-squares (LS) mean change in Least-squares mean change from baseline Primary endpoint averaged over weeks 22, 23, and 24 Secondary endpoint weeks 22 and 24

	Placebo (n = 76)	**Nipocalimab (n =77)**	**Between group difference**
MG-ADL (Primary endpoint)	-3.25	-4.70	-1.45 (p=0.0024)
QMG (Secondary endpoint)	-2.05	-4.86	-2.81 (p=0.00012

[redacted]

These changes were not only statistically significant, but they were clinically significant as well (MCID for MG-ADL and QMG are 2 and 3 points respectively).

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	History of serious hypersensitivity reaction to nipocalimab or its excipients
Other Warnings	Infections: Increased risk of infection. In clinical trials, serious infections were reported in 7% of patients. Delay administration in patients with an active infection. Hypersensitivity Reactions: Reactions including anaphylaxis, angioedema, rash, urticaria, and eczema have occurred. If a reaction occurs, the infusion should be discontinued. Infusion-Related Reactions: Reactions such as headache, rash, nausea, and chills have been observed. If a severe reaction occurs, the infusion should be discontinued. Mild to moderate reactions can be considered for rechallenge with close observation, slower infusion rate, and premedication. Patients should be monitored for 30 minutes after each infusion for infusion related or hypersensitivity reactions Vaccination considerations: Live or live-attenuated vaccines are not recommended during treatment with nipocalimab.
Top AEs	The most common adverse reactions (≥10%) reported were respiratory tract infections (18%), peripheral edema (12%), and muscle spasm (12%), hypersensitivity reaction (8%), abdominal pain (8%), back pain (8%)
Drug Interactions	Nipocalimab may reduce the effectiveness of medications that bind to the neonatal Fc receptor. These include immunoglobulin products (e.g., IVIg) and monoclonal antibodies (regardless of indication).
Other Considerations	There is limited human data on the use of nipocalimab during pregnancy. However, because it reduces maternal IgG and can be transported across the placenta, especially in the third trimester, it may reduce passive immunity in the newborn for six months or more. Limited data from an investigational study show that nipocalimab is excreted in human colostrum and breastmilk in the first 8 days after birth. There is insufficient data on the effects of nipocalimab on the breastfed infant or on milk production.

	DRUG	VANF	CFU	Mechanism and Indication	Considerations and Dosing
TREATMENT ALTERNATIVES (newer MG Agents)	**Nipocalimab-aahu (IMAAVY®)**	TBD	TBD	Neonatal Fc Receptor Antagonist Generalized MG patients who are AChR+ or MuSK+	Infection, peripheral edema, muscle spasms, hypersensitivity, abdominal pain, and back pain IV infusion: Initial dose 30mg/kg Maintenance dose: 15mg/kg IV every 2 weeks (starting 2 weeks after initial dose)
	Rozanolixizumab-noli (RYSTIGGO®)	No	Yes	Neonatal Fc Receptor Antagonist Generalized MG patients who are AChR+ or MuSK+	Headache, infection, diarrhea, pyrexia, hypersensitivity reactions, and nausea Subcutaneous infusion given weekly for 6 weeks. Repeated as needed no more than 63 days from start of previous cycle. Repeat cycles may be common as MG symptoms can return to baseline as soon as 8 weeks after stopping treatment.
	Efgartigimod (Vyvgart®)	No	Yes	Neonatal Fc Receptor Antagonist Generalized MG patients who are AChR+	Allergic reactions, headache, infections, leukopenia, myalgia IV infusion given weekly for 4 weeks. Repeated as needed no more than 50 days from start of previous cycle. Repeat cycles are common as MG symptoms can return to baseline as soon as 8 weeks after starting a 4-week cycle.
	Efgartigimod/hyaluronidase (Vygart Hytrulo®)	No	Yes	Neonatal Fc Receptor Antagonist Generalized MG patients who are AChR+	Infection, injections site reactions, and headache Subcutaneous injection (prefilled syringe or vial) once weekly for 4 weeks. Repeated cycles as needed, based on clinical evaluation; symptoms may return to baseline after a cycle. Rotate injection sites; avoid live vaccines during treatment.
	Ravulizumab-cwvz (Ultomiris®)	No	Yes	Complement C5 Inhibitor Generalized MG patients who are AChR+	Infusion-related reactions, severe meningococcal infection (vaccination prior to therapy required), other infections, diarrhea, headache IV infusion with weight-based dosing every 8 weeks, starting 2 weeks after the loading dose
	Eculizumab and biosimilars	No	Yes	Complement C5 Inhibitor Refractory generalized MG patients who are AChR+	Infusion-related reactions, severe meningococcal infection (vaccination prior to therapy required), other infections, headaches, musculoskeletal pain IV infusion given weekly for 4 weeks then every 2 weeks
	Zilucoplan (ZILBRYSQ)	No	Yes	Complement C5 Inhibitor Generalized MG patients who are AChR+	Injection site reactions, upper respiratory tract infection, diarrhea, urinary tract infection, nausea/vomiting SubQ injection daily. Can be self-administered

	DRUG	VANF	Time to onset	Time to maximal effect
TREATMENT ALTERNATIVES (other chronic immunotherapies)	**Azathioprine**	F	12 months	1-2 years
	Cyclosporine	F	6 months	7 months
	Mycophenolate mofetil	F	6-12 months	1-2 years
	Prednisone	F	2-3 weeks	5-6 months
	Tacrolimus	F	6 months	12 months
	IVIg	F		Immediate
	Rituximab (biosimilar) (stronger evidence in MuSK+ gMG)	F	6-12 months	7-16 months
	Plasma exchange	F		immediate

VHA PLACE IN THERAPY		
	Potential Use in VHA	• Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder. The disease is characterized by fatigable weakness caused by antibodies that interfere with skeletal muscle signaling at the neuromuscular junction. Symptoms can be limited to the eyes (ocular MG) or systemic (generalized MG, gMG). In its most severe case, gMG can result in respiratory depression or respiratory failure. • It is estimated that there are ~80,000 people with MG in the United States. In the last 4 quarters, there were approximately 10,500 Veterans with MG who sought care at VA. • Nipocalimab joins efgartigimod and rozanolixizumab in the neonatal Fc receptor antagonist class. This class of medications offers fast-onset steroid-sparing control of gMG symptoms. • The Vivacity-MG Phase 2 study showed a dose-dependent reduction in MG-ADL scores, reduction in serum total IgG levels, and reduction in anti-AChR autoantibodies (the sample size of anti-MuSK-positive patients was insufficient to draw conclusions regarding anti-MuSK autoantibody reductions). • The Vivacity-MG Phase 3 study demonstrated clinically meaningful and sustained improvements in patient symptoms for up to 6 months with scheduled dosing of nipocalimab therapy was added to standard of care. • Nipocalimab is the first neonatal Fc receptor antagonist with pre-defined scheduled dosing; other neonatal Fc receptor antagonist (rozanolixizumab and efgartigimod) cycles are repeated when symptoms return to baseline or based on clinical evaluation. Additional research is evaluating the use of scheduled dosing of efgartigimod and rozanolixizumab; neither currently have FDA approved recurrent scheduled dosing. • The participation of rarer antibody types (MuSK+ and LRP4+) in the Vivacity-MG Phase 3 study was low, but does reflect the typical antibody distribution in gMG. • Both nipocalimab and rozanolixizumab are FDA-approved biologic therapies for MuSK+ gMG. Rituximab continues to be a commonly utilized, evidence-based, off-label therapy for this antibody subtype. • Nipocalimab is the first biologic therapy to include patients with LRP4+ gMG in its phase 3 study population. However, the number of patients in Vivacity-MG phase 3 who were LRP4+ was too small to draw conclusions about the efficacy of nipocalimab in this population and thus FDA approval does not include this antibody type in the indication. • Nipocalimab therapy may be considered a steroid-sparing treatment option in AChR+ or MuSK+ gMG patients when other traditional oral immunosuppressants like azathioprine, mycophenolate, and/or steroids are ineffective. • Nipocalimab should not be combined with other IgG-affecting agents for chronic management, including intravenous immunoglobulin (IVIg), rozanolixizumab or efgartigimod. It can also decrease the efficacy of any monoclonal antibody therapy (regardless of indication), which may be a deciding factor for use depending on the patient's other medications. • There is no evidence to support nipocalimab in antibody-negative patients.

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References

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