Faricimab-svoa (VABYSMO) Intravitreal Injection
National Drug Monograph
July 2022
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

Description/Mechanism of Action
- Faricimab is a bispecific antibody that acts through inhibition of 2 different pathways, vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2). It is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME)

Dosage Form(s) Under Review
- Injection: 120 mg/mL solution in a single-dose vial
- Neovascular (Wet) Age-Related Macular Degeneration (nAMD): The recommended dose is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection (IVT) every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography (OCT) and visual acuity (VA) evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via IVT on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48 or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when faricimab was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly
- Diabetic Macular Edema (DME): Recommended to be dosed by following one of these two dose regimens:
  1. 6 mg administered by IVT every 4 weeks (approximately every 28 days ± 7 days, monthly) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central subfield thickness (CST) of the macula as measured by OCT is achieved, then the interval of dosing may be modified by extensions of up to 4-week interval increments or reductions of up to 8-week interval increments based on CST and VA evaluations through week 52
  2. 6 mg dose can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via IVT at intervals of every 8 weeks (2 months) over the next 28 weeks. Although additional efficacy was not demonstrated in most patients when dosed every 4 weeks compared to every 8 weeks, some patients may need every 4-week (monthly) dosing after the first 4 doses. Patients should be assessed regularly.

Clinical Evidence Summary

Efficacy Considerations
Neovascular (Wet) Age-Related Macular Degeneration

Two identically designed 48-week, phase 3 trials (TENAYA and LUCERNE) evaluated 1,329 newly diagnosed, treatment naïve patients with CMV secondary to nAMD.

Patients were randomized in a 1:1 ratio to aflibercept 2 mg administered fixed every 8 weeks (Q8W) after three initial monthly doses OR faricimab 6 mg every 4 weeks (approximately every 28 ± 7 days) for the first 4 doses, followed by OCT and VA evaluations 8 and 12 weeks later to determine whether to give a 6 mg dose on one of the following three regimens:

1) Weeks 28 and 44; (referred to as Q16W dosing)
2) Weeks 24, 36 and 48 (referred to as Q12W dosing)
3) Weeks 20, 28, 36 and 44 (referred to as Q8W dosing)

The study was designed to show non-inferiority for the primary endpoint of change in best corrected visual acuity (BCVA) score averaged over weeks 40, 44, and 48.

Demographics and baseline Information:

- Mean age 76 years; 40% male; 87% White; 56% phakic; IOP 15mmHg
- Best-corrected visual acuity, Early Treatment Diabetic Retinopathy Study (BCVA, ETDRS) 60 letters; BCVA categories: >/= 74 (14%), 73-55 (57%), </= 54 (29%)
- Central subfield thickness (CST) 357µm; presence of intraretinal fluid (IRF) 45%; presence of subretinal fluid (SRF) 66%
- Choroidal neovascularization (CNV) location (subfoveal 59%, juxtafoveal 25%; extrafoveal 14%); CNV lesion type (occult 50%, classic 27%, minimally classic 9%, RAP 5%, predominantly classic 4%); total area of CNV lesion 4.5mm2

Efficacy results are shown in **Table 1**. Faricimab at fixed intervals of up to every 16 weeks was found to be noninferior to aflibercept every 8 weeks.

Secondary outcomes not shown in table found that changes from baseline in total area of CNV lesion and total area of leakage, and quality of life (NEI VFQ-25 composite) were comparable between faricimab and aflibercept.

Table 1: Outcomes for Neovascular Age-Related Macular Degeneration Trials at 48 Weeks

	TENAYA		LUCERNE		
	Faricimab (n=334)	**Aflibercept (n=337)**	**Faricimab (n=331)**	**Aflibercept (n=327)**	**Comments**
Change from baseline in BCVA score	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)	• Outcomes were not analyzed according to treatment interval • No studies comparing faricimab to aflibercept using treat and extend protocols • Durability of extended dosing intervals unknown. Long-term studies are ongoing (year 2 data and long-term follow-up in 2-year open-label extension study)
Treatment difference	0.7 (-1.1, 2.5)		0.0 (-1.7, 1.8)		
BCVA Snellen equivalent 20/40 or better (% pts)	56.4	57	55.2	49.4	
Gain of >15/≥10/≥5/≥0 EDRS letters (%pts)	20/37/59/76	16/32/58/77	20/39/61/82	22/36/59/79	
Avoided loss of ≥15 EDRS (%pts)	95.4	94.1	95.8	97.3	
Change in CST (µm)	-136.8	-129.4	-137.1	-130.8	
% patients completing 48 weeks of treatment on: Q8W/Q12W/Q16W interval	20/34/46	NA	22/33/45	NA	
Median number of doses through week 48	6	8	6	8	

Abbreviations: BCVA=best-corrected visual acuity; CST=central subfield thickness

Two-year data in nAMD (unpublished) show that more than 60% of patients receiving faricimab could be treated every 16 weeks and approximately 80% could be treated every 12 weeks or longer while maintaining comparable visual gains and reduction in CST versus aflibercept administered every 8 weeks. This a 15% increase in patients achieving extended dosing intervals since the analysis at one year.

Diabetic Macular Edema

Two identically designed 1-year, phase 3 trials (YOSEMITE and RHINE) evaluated 1,891 patients with center-involving macular edema secondary to type 1 or type 2 diabetes.

Patients were randomized 1:1:1 to

- Faricimab 6mg every 4 weeks for 6 injections, then fixed dosing every 8 weeks
- Faricimab 6mg every 4 weeks for 4 injections, then adjustable dosing (based on treat and extend) per protocol up to every 16 weeks referred to as personalized treatment interval (PTI)
- Aflibercept 2mg every 4 weeks for 5 injections, then fixed-dosing every 8 weeks

The study was designed to show non-inferiority for the primary endpoint of change in best corrected visual acuity (BCVA) score at year one averaged over weeks 48, 52, and 56.

Demographics and baseline Information:
Mean age 62 years; 60% male; 78% White; type 2 diabetes 94%; A1C 7.6%; SBP 137mmHg; 75% phakic; anti-VEGF naïve 78%; time since DME diagnosis 18 months; BCVA, EDRS 62 letters; CST 480µm; macular ischemic non-perfusion 40%; macular leakage 95%; DR absent or questionable or mild to moderate non-proliferative diabetic retinopathy (NPDR) 57%; Moderately severe to severe NPDR 33%.

Faricimab Q8W and PTI were found to be noninferior to aflibercept. Macular edema was reduced in a slightly greater percentage of patients compared to aflibercept. Over 98% avoided loss of 15 or more EDRS letters in all treatment groups. 96-98% of patients had absence of SRF at week 52. Two-year data (Data on file Genentech) show continued improvement in all treatment groups (Table 2a).

Outcomes were similar between faricimab Q8W and PTI dosing. Approximately 72% of patients achieved Q12 or Q16 week dosing In the faricimab PTI group.

Table 2: Outcomes for Diabetic Macular Edema Trials at 1-year

	YOSEMITE			RHINE			
	Faricimab* (n=315)	**Faricimab PTI (n=313)**	**Aflibercept* (n=312)**	**Faricimab* (n=317)**	**Faricimab PTI (n=319)**	**Aflibercept* (n=315)**	**Comments**
Change from baseline In BCVA score	10.7	11.6	10.9	11.8	10.8	10.3	• Outcomes were not analyzed according to treatment interval • No studies comparing faricimab to aflibercept using treat and extend protocols
BCVA Snellen equivalent 20/40 or better (% pts)	72	77	75	73	72	69	
Gain of >15/≥10/≥5/≥0 ETDRS letters (%pts)	29/57/79/92	36/58/80/95	32/58/81/91	34/59/82/92	29/53/77/91	30/54/78/91	
Change in CST (µm)	-206.6	-196.5	-170.3	-195.8	-187.6	-170.1	
Absence of DME weeks 48-56 (%pts)	77-87	80-82	64-71	85-90	83-87	71-77	
Absence of intraretinal fluid weeks 48-56 (%pts)	42-48	34-43	22-25	39-43	33-41	23-29	
>/= two-step ETDRS-DRSS improvement (%pts)	46	43	36	44	44	47	
% patients achieving Q4W/Q8W/Q12W/Q16W dosing at week 52	NA	11/15/21/53	NA	NA	13/16/20/51	NA	

Abbreviations: BCVA=best-corrected visual acuity; CST=central subfield thickness; DME=diabetic macular edema; DRSS-diabetic retinopathy severity scale; ETDRS=early treatment diabetic retinopathy study; PTI=personalized treatment interval
**Initial monthly dosing, followed by fixed-dosing every 8 weeks*

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Table 2a: Outcomes for Diabetic Macular Edema Trials at 2 years

	YOSEMITE			RHINE		
	Faricimab (n=315)	**Faricimab PTI (n=313)**	**Aflibercept (n=312)**	**Faricimab (n=317)**	**Faricimab PTI (n=319)**	**Aflibercept (n=315)**
Change from baseline In BCVA score	10.7	10.7	11.4	10.9	10.1	9.4
Gain of >/= 15 ETDRS letters (%pts)	37	38	37	40	31	39
Change in CST (µm)	-216	-204.5	-196.3	-202.6	-197.1	-185.6
Absence of DME weeks 92-100 (%pts)	86-92	78-86	73-81	88-93	85-98	80-84
Absence of intraretinal fluid weeks 92-100 (%pts)	59-63	43-48	33-35	56-62	45-52	39-45
Absence of subretinal fluid weeks 92-100 (%pts)	94-97	94-97	97	95-96	96-97	96
% patients achieving Q4W/Q8W/Q12W/Q16W dosing at week xx	NA	7/15/18/60	NA	NA	10/12/14/64	NA

Abbreviations: BCVA=best-corrected visual acuity; CST=central subfield thickness; DME=diabetic macular edema; DRSS-diabetic retinopathy severity scale; ETDRS=early treatment diabetic retinopathy study; PTI=personalized treatment interval

Safety Considerations

- **Boxed warnings:** None
- **Contraindications:**
  - Ocular or periocular infection
  - Active intraocular inflammation
  - Hypersensitivity to faricimab or excipients
- **Other warnings/precautions**:
  - Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
  - Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
  - There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.
- **Adverse reactions**
  - The most common adverse reaction (≥ 5%) reported in patients receiving faricimab was conjunctival hemorrhage (7%).
  - Other adverse events reported in the clinical trials shown in **Table 3**. Incidence of vitreous floaters, retinal pigment tear, and increased intraocular pressure was slightly greater in the faricimab group.

Table 3: Common Adverse Reactions in at least 1% of Patients

	Faricimab		Aflibercept	
	nAMD	**DME**	**nAMD**	**DME**
Conjunctival hemorrhage (%)	7	7	8	6
Vitreous floaters (%)	3	3	2	2
Retinal pigment tear (%)	3		1	
Increased intraocular pressure (%)	3	3	2	2
Eye irritation (%)	1	1	<1	1
Ocular discomfort (%)	1	1	<1	<1
Vitreous hemorrhage (%)	<1	1	1	<1

Data from product package insert

- **Immunogenicity:** As with all therapeutic proteins, there is a potential for immunogenicity with faricimab. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with faricimab. The clinical significance of anti-faricimab antibodies on safety is unclear. Immunogenicity was not assessed for aflibercept.

- **Patients with >/= 1 Serious Adverse Events (SAEs):**
  Ocular:
  - nAMD studies: 1.6% (faricimab) and 2.0% (aflibercept)
  - DME studies: 2.4% (faricimab Q8W), 3.0% (faricimab PTI), 1.3% (aflibercept)

  Non-ocular:
  - nAMD studies: 10.2% (faricimab) and 12.3% (aflibercept)
  - DME studies: 20.1% (faricimab Q8W), 16.3% (faricimab PTI), 16.3% (aflibercept)

  Deaths:
  - nAMD studies: 6 deaths in each group
  - DME studies: 1.9% (faricimab Q8W), 1.4% (faricimab PTI), 1.4% (aflibercept)
- **Other**
  Discontinuations due to an Adverse Event:
  - nAMD studies: 1.6% (faricimab) and 0.6% (aflibercept)
  - DME studies: 1.6% (faricimab Q8W), 1.9% (faricimab PTI), 1.4% (aflibercept)

  In all trials, there was no clustering of any one event.

Other Considerations

- Recruitment underway for studies in macular edema due to retinal vein occlusion

Other Therapeutic Options

Alternative anti-VEGF treatments are listed in **Table 4.**

Table 4: Anti-VEGF Treatment Options

Drug	Formulary Status	Approved Indications	Comments
Faricimab	TBD	nAMD, DME	• See dosing information on page 1. In clinical trials, approximately 75% of patients were on Q12W or Q16W dosing
Ranibizumab	F	nAMD, DME, DR, macular edema following RVO, mCNV	• Dosing for nAMD: 0.5mg monthly or 0.5mg monthly for 3 doses followed by less frequent dosing with regular assessment or 0.5mg monthly for 4 doses followed by every 3 months • Dosing for DME: 0.3mg monthly
Aflibercept	F	nAMD, DME, DR, macular edema following RVO	• Dosing for nAMD: 2mg monthly for 3 doses, followed by 2mg Q8W. Some patients may require monthly dosing. Although less effective than q8W, some may be treated Q12W after one year of effective therapy. • Dosing for DME: 2mg monthly for 5 doses, followed by 2mg Q8W. Some patients may require monthly dosing

Bevacizumab	NF	Off-label	• 1.25mg frequency of administration similar to ranibizumab
Ranibizumab implant	NF	nAMD	• Initial implant with refills every 24 weeks (approximately 6 months). • Requires surgical procedure for implantation. • Many safety concerns including boxed warning of a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab
Brolucizumab	NF	nAMD	• 6mg monthly for first 3 doses following by 6mg every 8-12 weeks • Concerns of reports of retinal artery occlusion

Abbreviations: DME=diabetic macular edema; DR=diabetic retinopathy; mCNV=myopic choroidal neovascularization; nAMD=neovascular age-related macular degeneration; RVO=retinal vein occlusion

Projected Place in Therapy

Studies show that faricimab can be doses every 12 or every 16 weeks in approximately 75% of patients with nAMD or DME. Two-year data indicate that the dosing intervals and outcomes were maintained. Clinical trials found faricimab to be noninferior to aflibercept dosed every 8 weeks and it does not appear to have adverse events that differ from aflibercept. There was no comparison with aflibercept using treat and extend or PRN protocols because FDA-approved dosing was used for aflibercept. The results for faricimab for those on Q8W, Q12W, and Q16W were pooled and not shown individually; therefore, it is unknown if there were any differences in outcomes among the 3 administration frequencies.

Faricimab has the potential to reduce treatment burden for patients and clinic staff. Faricimab is another treatment option for patients with nAMD or DME. It may be particularly useful for those who would benefit from reducing treatment burden (e.g., long travel times, physical mobility limitations, etc.).

References

Heier JS, Khanani AM, Quezada Ruiz C, Basu K, et al.; TENAYA and LUCERNE Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022 Feb 19;399(10326):729-740.

Wykoff CC, Abreu F, Adamis AP, Basu K, et al. YOSEMITE and RHINE Investigators Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet. 2022 Feb 19;399(10326):741-755.

VABYSMO (faricimab-svoa injection) for intravitreal use [prescribing information online]. San Francisco, CA: Genentech, Inc. January 2022. Available at: label (fda.gov)

New two-year data confirm Genentech's Vabysmo improves vision with fewer treatments for people with wet-age-related macular degeneration [press release]. South San Francisco, CA: Genentech Inc; July 14, 2022. https://www.gene.com/media/press-releases/14960/2022-07-14/new-two-year-data-confirm-genentechs-vab.

New Two-Year Data for Genentech's Vabysmo and Susvimo Reinforce Potential to Maintain Vision With Fewer Treatments for People With Two Leading Causes of Vison Loss
https://www.gene.com/media/press-releases/14944/2022-02-10/new-two-year-data-for-genentechs-vabysmo

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