Nerandomilast (JASCAYD)
National Drug Monograph
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VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services 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/Mechanism of Action

- Nerandomilast exhibits antifibrotic and immunomodulatory effects through preferential inhibition of the phosphodiesterase 4B (PDE4B) isoenzyme. PDE4B inhibition elevates intracellular cyclic adenosine monophosphate (cAMP) levels and reduces the expression of pro-fibrotic growth factors and inflammatory cytokines, which are overexpressed in idiopathic pulmonary fibrosis (IPF).

Indication(s) Under Review in This Document

- FDA approved indications: Nerandomilast is indicated for the treatment of IPF (October 2025) and non-IPF interstitial lung disease with progression, also known as progressive pulmonary fibrosis (PPF) (December 2025) in adult patients.

Dosage Form(s) Under Review

- **Dosage form:** 9 mg, 18 mg film-coated tablets
- **Usual dose:** 18 mg twice daily, administered every 12 hours without regard to food.
- **Reduced dose:** 9 mg twice daily in patients who are 1) unable to tolerate 18 mg twice daily or 2) receiving concomitant strong CYP3A4 inhibitors.
- **Dose in patients also receiving pirfenidone:** 18 mg twice daily; <u>do not dose reduce</u> (due to drug interaction, see Other Considerations)
- **How supplied:** Bottles of 60 tablets

Clinical Evidence Summary

Efficacy Considerations - IPF

- FDA approval of nerandomilast for IPF was based on two randomized, double-blind, placebo-controlled, multinational, industry-sponsored trials in patients 40 years of age or older with IPF, one phase 2 and one phase 3 study. In both trials, patients were diagnosed with IPF by the investigator according to guidelines based on high-resolution computed tomographic (CT) scan and confirmed centrally. Antifibrotic therapy with stable doses of pirfenidone or nintedanib was permitted. The primary endpoint was change from baseline in forced vital capacity (FVC) at 12 weeks (phase 2 study) and 52 weeks (phase 3 study, FIBRONEER-IPF). See Tables 1 and 2 for more details.
- FIBRONEER IPF (Phase 3, n=1,117)
    - <u>Key exclusions</u>: Patients with active vasculitis, severe depression, suicidal behavior or ideation, prebronchodilator forced expiratory volume in one second [FEV1]/FVC < 0.7, elevated hepatic transaminases >2.5 times the upper limit of normal, total bilirubin >1.5 times the upper limit of normal, estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m^2, and patients using

immunomodulatory medications (except oral corticosteroids at a prednisone equivalent dose of ≤15 mg daily) were excluded.

- Intervention: Patients were randomized 1:1:1 to nerandomilast 18 mg twice daily, 9 mg twice daily, or placebo.
- Baseline/disposition: Characteristics were well-matched between groups. The mean age of the population was 70 years, and over 80% were male. Patients had been diagnosed with IPF an average of 3.5 years earlier. About 78% of patients were receiving antifibrotic therapy at baseline (nintedinib or pirfenidone). Eighty-one to 83% of patients completed the trial.
- Results:
  - Both doses of nerandomilast were associated with a smaller decline in mean FVC vs. placebo over 52 weeks. An effect was noted soon after randomization and continued throughout the study period.
  - No improvement was observed with nerandomilast vs. placebo for secondary endpoints including acute exacerbations, quality of life, or death.

- In the exploratory phase 2 trial in patients with IPF, 147 patients were randomized 2:1 to receive nerandomilast 18 mg twice daily or placebo. Nerandomilast appeared to maintain FVC compared to a decline in FVC observed in the placebo group as evaluated over a 12-week treatment period.

Table 1: Selected Baseline Characteristics/Disposition from FIBRONEER-IPF

	NERA 18 mg N=392	NERA 9 mg N=392	PBO N=393
FVC mean (mL)	2827	2837	2864
FVC % of predicted	78	79	78
DLco mean (%)	52	52	50
On antifibrotic tx (%)	78	78	78
Nintedanib (%)	45	47	44
Pirfenidone (%)	32	31	34

Table 2: Primary Endpoint Results from FIBRONEER-IPF

	NERA 18 mg N=392	NERA 9 mg N=392	PBO N=393
Δ FVC from baseline (mean, mL)	-115	-139	-184
Nerandomilast monotherapy (mL)	-79	-70	-149
+Nintedanib at baseline (mL)	-119	-131	-192
+Pirfenidone at baseline (mL)	-134	-202	-197

Efficacy Considerations - PPF

- FDA approval of nerandomilast for the PPF indication was based on one randomized, double-blind, placebo-controlled, multinational, industry-sponsored trial (FIBRONEER-ILD) that evaluated efficacy and safety of nerandomilast in 1,176 patients 18 years and older with a non-IPF interstitial lung disease (ILD) diagnosis and predefined criteria for progression. The primary endpoint was absolute decline in FVC from baseline at 52 weeks.
  - Key inclusion criteria: Patients had to have a diagnosis of ILD (other than IPF), fibrotic lung disease ≥10% by high-resolution computed tomographic (CT) scan within past 12 months, FVC ≥45% of predicted, and DL_{CO} of ≥25% of predicted. Within the prior 24 months, patients had to have one of

the following: a relative FVC decline of ≥10%; an FVC decline of 5 to 10% with worsening respiratory symptoms and/or an increased extent of fibrotic changes on imaging; or worsening respiratory symptoms and increased extent of fibrotic changes on imaging. Patients who were on stable doses of nintedanib or certain immunosuppressants (e.g., azathioprine, methotrexate) at baseline were permitted to enroll.

- Key exclusion criteria: Patients with active vasculitis, severe depression, suicidal behavior or ideation, elevated hepatic transaminases >2.5 times the upper limit of normal, total bilirubin >1.5 times the upper limit of normal, estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m^2, and patients using certain immunomodulatory medications (prednisone equivalent dose of >15 mg daily, cyclophosphamide, tocilizumab, mycophenolate, pirfenidone, rituximab) were excluded.
- Intervention: Patients were randomized 1:1:1 to nerandomilast 18 mg twice daily, 9 mg twice daily, or placebo.
- Baseline/disposition: Baseline characteristics were similar between groups. The mean age of the population was 66 years, and 56% were male. Patients had been diagnosed with ILD an average of 4.2 years earlier. Approximately 43% of patients were receiving nintedanib antifibrotic therapy at baseline. Eighty percent of patients completed the trial. Mean duration of exposure was about 14 months.
- Results:
  - Both doses of nerandomilast were associated with a smaller decline in mean FVC vs. placebo over 52 weeks (See Table 3)
  - No significant improvement was observed with nerandomilast vs. placebo for the key secondary endpoint of time to first acute ILD exacerbation, respiratory hospitalization, or death, or other endpoints including quality of life.

Table 3: Selected Baseline Characteristics/Disposition from FIBRONEER-ILD

	NERA 18 mg N=391	NERA 9 mg N=393	PBO N=392
FVC mean (mL)	2381	2326	2354
FVC % of predicted	70	70	70
DLco mean % of predicted	49	49	50
ILD diagnosis (%)			
Autoimmune ILD	29	29	26
Hypersensitivity pneumonitis	19	21	20
Unclassifiable idiopathic interstitial pneumonia	19	19	21
Idiopathic nonspecific interstitial pneumonia	21	19	19
Other ILD	13	25	28
On nintedanib (%)	44	44	43

Table 4: Primary Endpoint Results from FIBRONEER-ILD

	NERA 18 mg N=390	NERA 9 mg N=390	PBO N=391
Δ FVC from baseline (mean, mL)	-99	-85	-166
Placebo adjusted difference (mean, mL)	67	81	n/a

No nintedanib at baseline (mL)	-95	-82	-154
+Nintedanib at baseline (mL)	-103	-88	-181

Safety Considerations

Safety Results from Clinical Trials:

- For the original FDA approval of nerandomilast (IPF setting), the safety of nerandomilast was largely based on data from FIBRONEER-IPF, with supportive data from the phase 2 study. The median duration of exposure for study treatment was ~14 months in FIBRONEER-IPF and ~12 weeks in the phase 2 study. For the subsequent FDA approval in the PPF setting, safety data from FIBRONEER-ILD was evaluated.
- **Boxed warnings:** none
- **Contraindications:** none
- **Other warnings / precautions**: none

Table 5. Common Adverse Reactions from FIBRONEER-IPF and FIBRONEER-ILD

	FIBRONEER-IPF			FIBRONEER-ILD		
Adverse Reaction	**NERA 18 mg N=392 (%)**	**NERA 9 mg N=392 (%)**	**PBO N=393 (%)**	**NERA 18 mg N=391 (%)**	**NERA 9 mg N=393 (%)**	**PBO N=392 (%)**
Adverse reaction leading to DC*	15	12	11	10	8	10
Diarrhea	42	31	17	37	30	25
Monotherapy	26	17	8	27	15	16
+Nintedanib	62	49	27	49	48	37
+Nintedanib and DC due to adverse reaction*	13	2	1	11	9	10
+Pirfenidone	23	13	8	n/a	n/a	n/a
Cough	NR	NR	NR	15	13	14
COVID-19	13	16	12	11	10	15
Upper respiratory tract infection	13	11	10	12	10	15
Depression	12	11	10	10	10	11
Decreased weight	11	10	8	11	7	6
Decreased appetite	9	9	5	NR	NR	NR
Nausea	8	9	7	10	8	6

*Diarrhea was the most common adverse reaction that led to treatment discontinuation and occurred more frequently in patients on nerandomilast plus nintedanib.

- **Adverse events of special interest:** Due to known risks with other PDE4 inhibitors (roflumilast and apremilast), the following adverse events were closely evaluated in the FIBRONEER-IPF trial and discussed in the FDA Review.
    - **Vasculitis** –A signal was identified in the nonclinical development program. Patients with active vasculitis were excluded from the RCTs. Vasculitis was reported infrequently; however, there was a numeric excess of adjudicated vasculitis cases in nerandomilast-treated patients vs. placebo (5 cases vs. 1 case).

- **Psychiatric adverse events** –There is an increased risk of adverse psychiatric effects including suicidality associated with other PDE4 inhibitors (e.g., roflumilast, apremilast). Patients with severe depression or suicidal behavior or ideation were excluded from RCTs. Depression was the most commonly reported psychiatric adverse event in the IPF population and occurred more frequently in the nerandomilast groups vs. placebo. Depression more often led to treatment discontinuation with nerandomilast compared to placebo. There were few reports of suicidal ideation in all treatment groups.
- **GI adverse events –** In addition to the known GI adverse effects of PDE4 inhibitors (apremilast, roflumilast), GI adverse effects are also known to occur with the other antifibrotics, nintedanib and pirfenidone, frequently used in combination with nerandomilast during the clinical trials. The most reported GI adverse event was diarrhea. There was also an excess of other GI adverse events with nerandomilast. There was no signal of an excess of serious adverse events, but there was reduced tolerability, mainly due to diarrhea. Diarrhea generally occurred within the first three months of treatment.
- **Decreased appetite and weight:** Decreases weight and appetite were more frequent in patients treated with nerandomilast compared to placebo. Reductions in weight occurred most often in patients receiving the combination of nerandomilast plus nintedanib.

- **Discontinuations due to adverse events** were more common with nerandomilast vs. placebo (with and without additional antifibrotic therapy).
- **Serious adverse events** occurred in 34% of patients overall with no concerning signals according to the FDA review.
- **Deaths:** There were no excess deaths in the nerandomilast treatment groups in FIBRONEER-IPF and no concerning signals according to the FDA review.

Other Considerations

- **Drug Interactions:**
  - Strong CYP3A inhibitors: Reduce nerandomilast dose to 9 mg twice daily due to increased exposure of nerandomilast.
  - Moderate or strong CYP3A inducers: Avoid concomitant use due to decreased exposure of nerandomilast.
  - Pirfenidone: Recommend full nerandomilast dose of 18 mg twice daily when nerandomilast is prescribed with pirfenidone. Do not reduce dose of nerandomilast due to reduced exposure.
- **Pregnancy**: Based on animal studies, nerandomilast may increase risk of fetal loss. There are no available data on the use of nerandomilast in pregnant woman.

Other Therapeutic Options

Alternative treatments for IPF and non-IPF ILD are listed in table 6 below.

Drug	Nerandomilast JASCAYD	Pirfenidone ESBRIET	Nintedanib OFEV
FDA approval	2025	2014	2014
VANF status	TBD	NF with CFU	NF with CFU
Generic availability	No	Yes	No (estimated ~2029)
Mechanism of action	PDE4B inhibitor	Unclear; multiple effects including antifibrotic, anti-inflammatory, antioxidant	Tyrosine kinase inhibitor
FDA approval	• IPF • PPF	IPF	• IPF • PPF • Systemic sclerosis-associated ILD (SSc-ILD)
Dose/ administration	• 18 mg tablets BID, q12h; dose reductions to 9 mg for intolerability of higher dose.	• Target dose: 801 mg TID; (Initial dose 267 mg TID, titrated over weeks to target dose)	• Dose: 150 mg capsules BID, q12h with food; (↓ dose to 100 mg BID for tolerability concerns)
Efficacy	• IPF – 24% to 38% relative reduction in FVC decline in FVC vs. PBO (78% on add'l antifibrotic) • PPF – 40% to 48% relative reduction in FVC decline vs. PBO (44% on add'l antifibrotic)	• IPF - ~45% relative reduction in FVC decline vs. PBO at 52 wks (Δ193 ml, ASCEND)	• IPF - ~50% relative reduction in FVC decline vs. PBO at 52 wks (Δ 94 to 125 mL in 2 phase 3 studies); 1 of 2 phase 3 studies showed ↓ in acute IPF exacerbations (INPULSIS 1 and INPULSIS 2) • PPF –~57% relative reduction in FVC decline vs. PBO at 52 wks (Δ 107 mL) • SSc-ILD – ~44% relative reduction in FVC decline vs. PBO (Δ 41 mL)
Side effect profile	Diarrhea (affects tolerability, worse in combo with nintedanib), decreased weight, decreased appetite, depression	Warnings include: liver toxicity requiring monitoring, photosensitivity, severe cutaneous adverse reactions, GI disorders including nausea, vomiting, GERD, diarrhea	Warnings include: liver toxicity requiring monitoring, GI disorders including diarrhea, nausea, vomiting, embryofetal toxicity, bleeding
DDIs	CYP3A4 inducers and inhibitors; pirfenidone reduces nerandomilast exposure	CYP1A2 inhibitors and inducers; decreased exposure in smokers	P-gp and CYP3A4 inhibitors and inducers; decreased exposure in smokers

Projected Place in Therapy

IPF

- IPF is the most common ILD of unknown cause, accounting for greater than 30% of ILD. Prevalence increases with age, with a median age of diagnosis of 65 years. IPF is more common in males. Patients typically present with progressive dyspnea on exertion, reduced exercise capacity, and often a chronic, nonproductive cough. Most patients experience an irreversible, progressive decline in lung function leading to respiratory failure and death, with a median estimated range of survival of two to five years (though there is wide interindividual variability).
- Confirmation of an IPF diagnosis requires exclusion of other identifiable causes of ILD, high resolution CT scan showing usual interstitial pneumonia (UIP) pattern or probable UIP pattern, or indeterminate pattern for UIP with histologic confirmation of IPF. Pulmonary function tests are used to assess the pattern and severity of disease.
- The incidence of IPF is increasing worldwide. In 2019, the annual incidence of IPF in U.S. Veterans was 725 cases per 100,000 person-years.
- Antifibrotic agents have been shown to reduce the decline in FVC and are guideline recommended as part of standard of care. Pirfenidone and nintedanib have been shown to reduce the annual decline in FVC by about 50% compared to placebo. The pivotal registry trials did not identify a mortality benefit, but meta-analyses suggest a possible reduction in death. There are no head-to-head studies of nintedanib and pirfenidone. Both agents carry a risk of liver toxicity requiring monitoring. Other notable adverse effects with nintedanib are diarrhea, other GI effects, embryofetal toxicity, and bleeding. Pirfenidone is associated with nausea, vomiting, gastroesophageal reflux disorders, photosensitivity, and dermatologic reactions.
- Nerandomilast is the third antifibrotic agent approved in the U.S. for IPF. In the FIBRONEER IPF trial where 78% of patients were receiving nintedanib or pirfenidone at baseline, nerandomilast was associated with a reduction in mean FVC decline over a 52-week period compared to placebo. The relative reduction in FVC decline was greater in patients on nerandomilast monotherapy (47 – 53%) than in patients on additional IPF treatment (32 – 38%). There was no improvement observed in acute exacerbations, quality of life, or death with nerandomilast. Nerandomilast was commonly associated with diarrhea, particularly when combined with nintedanib. Other notable adverse effects with nerandomilast were decreased weight, decreased appetite, and depression. Other adverse effects evaluated as potential class effects of PDE4 inhibitors included vasculitis and psychiatric adverse events.

PPF

- PPF is a pattern of disease progression that occurs in a subset of patients with non-IPF ILD. Patients with PPF experience worsening respiratory symptoms, decline in lung function, and risk of early death.
- PPF is defined by at least two of the following: worsening symptoms, evidence of physiological decline (lung function testing), or evidence of radiological progression. Specific criteria for progression may differ depending on the reference (e.g., American Thoracic Society Guidelines, FIBRONEER-ILD trial).
- It is estimated that 13 to 40% of patients with non-IPF ILD have a progressive fibrosing phenotype, representing up to 28 cases in 100,000 in the U.S.
- Nintedanib is indicated for the treatment of PPF. Nintedanib was associated with a reduction in mean FVC decline over a 52-week period of 57% vs. placebo and carries a conditional recommendation in the 2022 American Thoracic Society guidelines.
- Nerandomilast is the second agent approved in the management of PPF based on the results of the FIBRONEER-ILD trial. At 52 weeks, nerandomilast was associated with a relative reduction in decline of FVC 40 to 48% vs. placebo, with 44% of the population receiving concomitant nintedanib. No improvements were noted in the key secondary endpoint of time to first acute ILD exacerbation,

respiratory hospitalization, or death, or other endpoints including quality of life. Overall, nerandomilast was associated with a similar side effect profile as in the IPF population.

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