Brensocatib (BRINSUPRI) in Non-Cystic Fibrosis Bronchiectasis (NCFB)
National Drug Mini-Monograph
December 2025
VA Pharmacy Benefits Management Services and 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.

Abbreviations: BSI-bronchiectasis severity index, COPD=chronic obstructive pulmonary disease; DB=double-blind; LS=least squares mean change; MC=multicenter; MCID=minimally important clinical difference; NCFB=non-cystic fibrosis bronchiectasis; PC=placebo-controlled; R=randomized; PB FEV_1=postbronchodilator forced expiratory volume in 1 second; PBO=placebo, QOL=quality of life (assessed QOL-respiratory domain of the QOL-bronchiectasis questionnaire [QOL-B RSS); RR=rate ratio

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Competitive, reversible inhibitor of dipeptidyl peptidase 1 (DPP-1). DPP-1 is responsible for activation of pro-inflammatory neutrophil serine proteases (NSPs) during neutrophil maturation in bone marrow. NSPs are involved in the pathogenesis of neutrophil-mediated non-cystic fibrosis bronchiectasis (NCFB) inflammation.
Indication Under Review	Treatment of non-cystic fibrosis bronchiectasis (NCFB) in adults
Dosage Regimen	10-25 mg once daily
Dosage Forms Under Review	10 and 25 mg tablets

EFFICACY CONSIDERATIONS	
Trial[2]	**ASPEN (Phase 3)**
Design	R, DB, MC, PC x 52 weeks
Population	Adults (n=1680 adults and 41 adolescents with bronchiectasis (chronic cough or sputum production or recurrent respiratory tract infection [RTI]) confirmed by CT scan of the chest within the past 5 years. BMI ≥ 18.5 and ≥ 2 exacerbations* leading to antibiotic treatment within the last 12 months. Patients with asthma or COPD were excluded if respiratory symptoms were primarily caused by these diseases. If these conditions were considered secondary to bronchiectasis, enrollment was permitted (<20% of patients had a diagnosis of asthma or COPD). Also excluded were patients with bronchiectasis due to cystic fibrosis or suspected immunodeficiency disorder. Patients who were currently smoking and those receiving >12 hours per day of supplemental oxygen were also excluded. **Exacerbation defined as presence of ≥ 3 of the following symptoms for at least 48 hours leading to physician prescribing antibiotics: increased cough or sputum production, change in sputum consistency or increased sputum purulence, increased breathlessness, reduced exercise tolerance (or both), fatigue, malaise (or both) or hemoptysis leading to treatment with antibiotics. Exacerbations leading to treatment with intravenous (IV) antibiotics or hospitalization were considered to be severe.*
	Key baseline characteristics: Mean age: 60 years Female: 62.6-66% Long-term antibiotics: 23.6-26.8% Sputum sample + for pseudomonas aeruginosa: 34.8-35.7% Bronchiectasis Severity Index Score: 7.1 (range 0-26 with higher scores indicating more severe disease; 0-4=mild disease; 5-8 moderate disease; ≥ 9=severe disease) Postbronchodilator FEV_1 % predicted: 71.9 (placebo) vs. 74.4 (brensocatib) Blood eosinophils ≥ 300 cells/mm^3: <20% H/O COPD or Asthma: <20% Hospitalized for exacerbation past 24 months: 23.1-25.2 Patients who never smoked: 67.5-71.9%
	Brensocatib 10 or 25 mg once daily for 52 weeks.
Comparator	Placebo once daily for 52 weeks.

Results

ASPEN Trial

Outcome	Bren 10 mg (n=582)	Bren 25 mg (n=574)	Placebo (N=563)	Comments
Annualized rate of exacerbation	1.02 (0.91-1.13) RR=0.79 (0.68-0.92; adj p-0.004 **RRR 21%; ARR 0.27 events/yr**	1.04 (0.93-1.16) RR=0.81 (0.69-0.94); adj. p=0.005 **RRR 19%; ARR 0.25 events/yr**	1.29 (1.16-1.43)	
Time to 1st exacerbation	HR=0.81 (0.7-0.95); adj. p=0.02	HR=0.83 (0.7-0.97); adj. p=0.04		**# days not reported** RRR incidence of 1st exacerbation vs. PBO. 10 mg: 19%; 25 mg 17%
% exacerbation free	48.5% RR=1.2 (1.06-1.37); adj. p=0.02	48.5% RR=1.18 (1.04-1.34); adj. p=0.04	40.3%	
Mean change baseline in PB FEV_1	LS=minus 50 mL LS vs. PBO=11; adj. p=0.38 (NS)	LS=minus 24 mL LS vs. PBO=38; adj. p-0.04	LS=minus 62 mL	
Annualized rate of severe exac.	0.14 (0.1-0.18) RR=0.74 (0.51-1.09); N/A	0.14 (0.11-0.18) RR=0.74 (0.52-1.06); adj. p=0.21 (NS)	0.19 (0.14-0.24)	
Mean change baseline in QOL	LS=6.84 vs. PBO 2.03 (-0.08 to 4.14)	LS=8.58 vs. PBO 3.77 (1.68-5.85)	LS=4.81	No statistical analyses performed vs. PBO due to nonsignificant finding in earlier endpoint.

Outcomes were analyzed based upon a hierarchical statistical testing plan. No further statistical testing was done for subsequent outcomes after the initial nonsignificant finding.

Adult patients completed the Respiratory Symptoms domain of the Quality of Life-Bronchiectasis questionnaire (QOL-B RSS) at baseline and every 2 weeks (scores range: 0-100; higher scores indicate few symptoms; MCID=8 points) for 52 weeks.

Exploratory analyses: 1) annualized rate of exacerbations in specified subgroups; 2) change from baseline in PB forced vital capacity (FVC); 3) change from baseline in the average daily score of the Bronchiectasis Exacerbation and Symptoms Tool questionnaire or BEST (electronic diary every evening; scores range 0-26; lower scores indicating fewer symptoms; MCID=4 points). *If the algorithm in the "electronic symptom-capture" detected an increase in symptoms, the site and patient were notified of a potential exacerbation.*

Comments/ Questions

- Clinical practice guidelines advocate for ongoing antibiotic treatments in patients with NCFB but only 25% of patients at baseline were receiving antibiotics and >30% of patients with a + sputum sample for Pseudomonas aeruginosa.
- Can a difference in PB FEV_1 reduction of 38 mL vs. placebo over 52 weeks signal slower progression of disease? No clear difference between 10 and 25 mg brensocatib in any endpoint; only mean change in PB FEV_1 from baseline for the 25 mg dose vs. placebo, but is the difference clinically meaningful vs. 10 mg or placebo? Further studies are necessary to confirm slower progression of disease.
- Did the electronic symptom-capture algorithm notifying sites and patients of possible exacerbation influence decisions regarding treatment for exacerbation which was the primary endpoint?
- No difference in severe exacerbations between groups.

Authors' Conclusions

Brensocatib led to a lower annualized rate of exacerbations vs. placebo in patients with bronchiectasis. The decline in lung function was less with the 25 mg dose vs. placebo.

Trial[3] **WILLOW (Phase 2)**

Design R, DB, MC, PC x 24 weeks

Population

Adults 18-85 years of age with clinical history consistent with bronchiectasis (cough, chronic sputum production, or recurrent respiratory infection) confirmed by CT scan (n=256). Eligible patients were required to have ≥ 2 documented exacerbations* in the prior 12 months, a history of chronic sputum expectoration, sputum color rated as being mucopurulent or purulent and able to provide a sputum sample at screening.

Excluded: Patients with diagnosis of cystic fibrosis; immunodeficiency disorder (hypergammaglobulinemia, common variable immunodeficiency or alpha$_1$-antitrypsin deficiency) or primary diagnosis of asthma or COPD. Patients with severe periodontitis were also excluded because of the possible risk of therapy with brensocatib.

**Exacerbations were defined as similar to the ASPEN trial. Severe exacerbations led to hospitalization.*

Key baseline characteristics:

Mean age: 64 years

Females: 63-71%

Long-term macrolide use: 12-18%

Sputum sample + for pseudomonas aeruginosa: 33-38%

Median Bronchiectasis Severity Index score: 7-8 (moderate disease)

Exacerbations (≥ 3) in past 12 months: 28-41% (41% in brensocatib 25 mg)

Hospitalization for exacerbations past 24 months: 34-38%)

FEV_1 % predicted: 65.9-70%

History of COPD: 15-20%

History of Asthma: 22-29% (29% placebo)

Neutrophil elastase in sputum: <lower limit of quantification (LLOQ): 21-28%; LLOQ to <20 mcg/mL: 34-48% (placebo 48%) or ≥ 20 mcg/mL: 28-38%

Intervention

Brensocatib 10 mg or 25 mg once daily x 24 weeks

Comparator

Placebo once daily x 24 weeks

Results

WILLOW Trial

Outcome	Bren 10 mg (n=82)	Bren 25 mg (n=87)	Placebo (N=87)	Comments
Median time to 1st exacerbation	HR adj.=0.58 (0.35-0.95) vs. PBO; p=0.03	HR adj.=0.62 (0.38-0.99) vs. PBO; p=0.046	189 days	Median time to 1st exacerbation was low in brensocatib groups, so could not be estimated.
Rate of exacerbations /year (n)	34	42	54	% having ≥ 1 exacerbation: PBO: 48%; 10 mg: 32% (p=0.03 vs. PBO) and 25 mg: 33% (p=0.04 vs. PBO)
Incidence rate of exacerbation /year	0.88 (0.61-1.26) RR vs. PBO 0.64 (0.42-0.98); p=0.04	1.03 (0.75-1.42) RR vs. PBO 0.75 (0.5-1.3); p=0.17	1.37 (1.02-1.84)	
Mean change in screening PB FEV_1 (week 24)	LS=minus 0.3 percentage points	LS=minus 0.3 percentage points	LS=minus 1.8 percentage points	NS difference in LS mean change in percentage points from baseline vs. PBO (FEV_1 volume change not reported)
Mean change in baseline in QOL B-RSS vs. PBO	-2 (-3.9-0.02) NS	0.2 (-1.8-2.2) NS	-----	
Mean change in sputum conc. of active neutrophil elastase from baseline to 12 and 24 weeks	NR	NR	NR	Author notes conc. of active neutrophil elastase was lower in the active vs. PBO groups. No meaningful differences in response were found according to conc. of active neutrophil elastase between groups.

Comments	• Median time to 1st exacerbation: 25th percentile was 67 days placebo; 134 days 10 mg; 96 days 25 mg • Sensitivity analysis, that included the 25 patients who discontinued the trial and were considered as having an exacerbation, was consistent with the primary analysis. • Severe exacerbations (n): PBO=10; 10 mg=5; 25 mg=4 (no statistics reported)
Authors' Conclusions	Brensocatib prolonged the time to first exacerbation and was associated with a lower frequency of exacerbation vs. placebo in patients with bronchiectasis. Larger and longer-term trials are needed to examine the risks and benefits of brensocatib in these patients.

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings	Dermatologic adverse events including new rash or skin condition including dry skin and hyperkeratosis. If new rash or skin condition develops, refer to a Dermatologist for evaluation. Increased risk for gingival and periodontal effects. Patients should be advised to ensure they are performing routine dental hygiene and attending regular dental checkups. Effectiveness and safety of live attenuated vaccines is unknown when administered during treatment with brensocatib.
Top 5 AEs	Upper respiratory tract infection; headache, rash, dry skin, hyperkeratosis and hypertension.
Drug Interactions	Brensocatib is a substrate of CYP3A, P-glycoprotein and breast cancer resistance protein (BCRP). It is a weak inducer of CYP3A and an inhibitor of BCRP. • Strong CYP3A4 and P-glycoprotein inhibitors (clarithromycin 500 mg bid) increased Cmax of brensocatib by 68% and AUC by 55% after 6 days. • Moderate CYP3A4 and P-glycoprotein inhibitors (verapamil 240 mg daily) increased Cmax of brensocatib by 53% and AUC by 32% after 5 days. • Strong CYP3A4 inducers (rifampin 600 mg daily) reduced Cmax of brensocatib by 15% and AUC by 33% after 9 days. • Acid-reducing medications (esomeprazole 40 mg daily) did not affect brensocatib Cmax or AUC after 4 days. • CYP3A4 substrates (midazolam) no effect on the pharmacokinetics of either agent when used concomitantly with brensocatib.
Pregnancy	Studies evaluating the risk for major birth defects, miscarriage or other adverse maternal-fetal outcomes with brensocatib are not available.
Lactation	There is a lack of evidence of the presence of brensocatib or its metabolite in human milk, its effect on milk production or on the breastfed infant.
Trial Safety Results	Less common AEs but occurring more often than placebo include 1) gingival and periodontal AEs (WILLOW study: 10 mg=9.9, 25 mg=10.1 vs. placebo=2.4%), 2) liver function test elevation (ASPEN study: ALT >3xULN: 10 mg=1.2%, 10 mg=0.9% vs. placebo=0; AST>3xUNL: 10 mg=0.3%, 25 mg=0.5% vs. placebo=0.2%; Alk Phos>1.5xULN: 10 mg=4.1%, 25 mg=4% vs. placebo 2.5%, 3) skin cancer (ASPEN study: 10 mg=0.5%, 25 mg=1.9% vs. placebo 1.1%) and 4) alopecia (ASPEN study: 10 mg=1.5%, 25 mg=1.6% vs. placebo=0.4%) Although pneumonia occurred in a 5.9% in placebo; 4% 10 mg and 4.7% 25 mg, severe infection was reported in 0.7% in placebo and 10 mg and 1.2% in the 25 mg group. FDA review noted that gingival and periodontal AEs were not statistically higher with brensocatib vs. placebo in the ASPEN trial which could be explained by less robust monitoring vs that done in the WILLOW trial. Dose-related AEs include AST/ALT elevation (resolving upon discontinuation), upper respiratory infection, headache, rash, dry skin and hyperkeratosis (ASPEN trial: 1.4% in 10 mg; 3% in 25 mg and 0.7% placebo). AEs resulting in death occurred in 3 patients 10 mg, 4 in the 25 mg and 7 patients on placebo. No causation reported.

OTHER CONSIDERATIONS	
FDA Review[4]	• Sufficient evidence from 2 clinical trials to support that the 10 and 25 mg brensocatib once daily statistically improves the following outcome measures: annualized rate of exacerbations, time to first exacerbation and percentage of patients who remain exacerbation free during the trial period. Additionally, there were statistical improvements in post-bronchodilator (PB) FEV_1 with the 25 mg but only a trend with the 10 mg dose. **However, the size of the treatment effect on PB FEV_1 was comparable for both doses.** *"The treatment difference for the 25 mg vs. placebo was too small to be clinically meaningful or to justify exclusion of the 10 mg dose." "Approval of the 25 mg dose is justified by the generally favorable safety profile and because of the significant improvement in FEV_1 with the 25 mg dose suggests some patients may gain additional benefit from the 25 mg dose."* • The applicant initially proposed approval of only the 25 mg dose based upon the evidence. However, additional analyses demonstrated that the difference in effect size between the 2 doses was even smaller than the earlier analysis showed. The review team found both doses to be clinically comparable and differences not clinically meaningful. Statistical differences between the doses in PB FEV_1 vs. placebo were not enough to exclude approving the 10 mg dose. Especially considering the potential dose-dependent AEs (Refer to safety section).
ICER Review[5]	• In the ASPEN Phase 3 trial population, there was not a clear difference between brensocatib and placebo among individuals with FEV1 <50%, BSI =9 (Bronchiectasis Severity Index [BSI] score [ranges from 0 to 26; 0-4=mild; 5-8=moderate; ≥9=severe disease] where a higher score is more severe), or asthma. Therefore, there remains residual uncertainty about the efficacy of brensocatib among more symptomatic patients with more advanced lung damage and/or asthma. • More than half of patients in the ASPEN trial were receiving inhaled corticosteroids. Although this is a common practice, it is discouraged in clinical practice guidelines. • Patients interviewed for the report cited the burdens and consequences of antibiotics. Whether brensocatib reduces the need for long-term antibiotics remains an important unresolved question. • Patients reported a substantial burden of airway clearance at home as well as limitations on work and travel related to airway clearance as important problems. Whether brensocatib reduces the need for these treatments and/or allows patients with NCFB more flexibility with work, travel, and social activities remains an important unresolved question. • The observed difference in absolute reduction in deterioration with brensocatib 25 mg (PB FEV1) vs. placebo is very small from a clinical perspective and likely not meaningful unless associated with larger changes over time. • ICER acknowledges that while reduction in exacerbations is very important for patients, daily symptoms such as fatigue and side effects of medications even when stable are also important. The effect of brensocatib at reducing symptom burden is unclear. The improvement in quality of life as measured by the Quality of Life-Bronchiectasis Respiratory Symptom Scale questionnaire observed in the intervention arms of ASPEN crossed the MCID threshold in terms of change from baseline (8 points) in the 25 mg brensocatib group, but between-group differences were less than what has been considered clinically meaningful in prior NCFB interventional trials (MCID 4 points). • Similarly, any improvement in symptoms as reported by the exploratory BEST score between brensocatib and placebo also did not reach a proposed MCID (4 points). • Treatment with brensocatib is rated as moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit ("B+"). • Although no concerning safety signals were noted, ASPEN was underpowered to detect rare safety events with brensocatib and safety should continue to be monitored. • Conclude that brensocatib is not cost-effective at current pricing.
NICE Review[6]	In process. Questions to be considered include place in therapy, does the eligible population in the clinical trials align with the definition used in clinical practice of patients with moderate to severe NCFB; which treatments are currently regarded as "established" to improve symptoms of the disease; is the published evidence interpreted as having the potential to substantially improve health benefits, etc.
Miscellaneous	Bell SC, et al: 20% Relative risk reduction in annualized exacerbations with brensocatib is similar to reductions observed with IV antibiotics (22%) but less than with oral macrolides (42%). However, differences in trials and the lack of direct comparisons prevent conclusions regarding comparative effectiveness. Since only 20% of patients were receiving long-term macrolide therapy, it is unknown whether brensocatib may improve outcomes when added to macrolides. However, it is possible that brensocatib may be an option in patients unable to take long-term macrolides. Author calls for comparative trials of brensocatib with guideline-based long-term antibiotics and for trials incorporating validated bronchiectasis phenotypes and endotypes in study designs to better define the role for these new anti-inflammatory medications for bronchiectasis.[7]

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES
Azithromycin	Yes	No	Supported by multiple Guidelines[8]	See reference 8

POTENTIAL PLACE IN THERAPY OF ——

1. Patients with a diagnosis of NCFB (e.g., clinical symptoms for at least 3 months [chronic cough, purulent sputum production] and confirmed by CT scan) who have experienced $\geq$ 2 exacerbations in the prior year despite use of chronic macrolide therapy or unable to use macrolides or inhaled antipseudomonal antibiotic. Since patients with a primary diagnosis of COPD or asthma were excluded from the trials, brensocatib should not be used in patients with these conditions until more evidence is available. Subgroup analyses (reported by ICER) showed no benefit of brensocatib in patients with PB FEV_1 <50%; BSI $\geq$ 9 and/or with an asthma diagnosis.
2. Whether brensocatib reduces the need for long-term antibiotics or improves symptoms of fatigue, malaise, etc. or quality of life has not been established.

References:

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References

1. Brensocatib Tablets BRINSUPRI prescribing information. Insmed Incorporated, Bridgewater NJ 08807. August 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217673s000lbl.pdf (Accessed September 2025)
2. Chalmers JD, Burgel PR, Daley CL, et al. Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med 2025;392:1569-1581.
3. Chalmers JR, Haworth CS, Metersky ML, et al. Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med 2020;383:2127-2137.
4. FDA Review of Brensocatib BRINSUPRI: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/217673Orig1s000IntegratedR.pdf (Accessed September 2025)
5. Wasfy JH, Kim K, Touchette DR, McKenna A, Richardson M, Herce-Hagiwara B, Kim S, Philips M, Ollendorf D. Brensocatib for Non-Cystic Fibrosis Bronchiectasis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, October 30, 2025**.** https://icer.org/wp-content/uploads/2025/10/ICER_NCFB-Final-Report_For-Publication_103025.pdf (Accessed October 2025).
6. https://www.nice.org.uk/guidance/gid-ta11564/documents/draft-scope-post-referral (Accessed September 2025).
7. Bell SC, Grimwood K. Brensocatib in Bronchiectasis – A New Sheriff in Town? N Engl J Med 2025;392:1647-1648. (Editorial)
8. Barker AF, Karamooz E. Non-Cystic Fibrosis Bronchiectasis in Adults. A Review. JAMA 2025;334:253-264.