CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217673
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Reviewer Name	Stephanie Olumba, PharmD, MPH, BCPS
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	August 8, 2025
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	Brensocatib
Trade Name	Brinsupri
Name of Applicant	Insmed Inc.
Therapeutic Class	dipeptidyl peptidase 1 (DPP1) inhibitor
Dosage Form(s)	10 mg and 25 mg tablets
Dosing Regimen	10 mg or 25 mg once daily with or without food

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Brinsupri (brensocatib) is necessary to ensure the benefits outweigh its risks. Insmed, Inc. (Applicant) submitted a New Drug Application (NDA) 217673 with the proposed indication for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older. The risks associated with brensocatib are dermatologic adverse reactions, gingival and periodontal adverse reactions, and live attenuated vaccines. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Pulmonology, Allergy, and Critical Care (DPACC) have determined that a REMS is not needed to ensure the benefits of brensocatib outweigh its risks. The benefit-risk profile is favorable, and the risks will be communicated in the Warnings and Precautions section of labeling. The proposed label advises healthcare providers to monitor patients for the development of new rashes or skin conditions and refer patients to dermatologist for evaluation of new dermatologic findings. Additionally, the proposed label advises healthcare providers to avoid use of live attenuated vaccines with brensocatib and to refer patients to dental care services for regular dental checkups while taking brensocatib. The expected prescribers of brensocatib are pulmonologists who are expected to be able to monitor and educate patients on these risks and refer patients to dermatologists or dentists as needed.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Brinsupri (brensocatib) is necessary to ensure the benefits outweigh its risks. Insmed, Inc. (Applicant) submitted a New Drug Application (NDA) 217673 for Brinsupri with the proposed indication for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older. This application is under review in the Division of Pulmonology, Allergy, and Critical Care (DPACC). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Brinsupri (brensocatib), a new molecular entity,[a] is a dipeptidyl peptidase 1 (DPP1) inhibitor proposed for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older. DPP1 activates pro-inflammatory neutrophil serine proteases (NSPs) during neutrophil maturation in the bone marrow. Activated NSPs are implicated in the pathogenesis of neutrophil-mediated NFCB inflammation. In cell-based assays, DPP1 inhibition by brensocatib reduces the activity

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

of NSPs including neutrophil elastase, cathepsin G, and proteinase 3.[1] Brensocatib is proposed to be supplied as tablets for oral administration in 10 mg and 25 mg dosage strengths. The proposed dosage for Brinsupri is 10 mg or 25 mg orally once daily with or without food.[1,b] Brinsupri is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217673 relevant to this review:

- **12/12/2024**: NDA 217673 submission received for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older.
- **03/26/2025**: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that thus far, no major safety concerns have been identified. There was no discussion of a REMS for brensocatib.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic lung condition characterized by persistent airway inflammation, structural airway damage, and irreversible dilation of the bronchi. While NCFB can be caused by a variety of factors, it is not caused by cystic fibrosis. Conditions that can lead to NCFB include autoimmune diseases (e.g., Sjogren's syndrome and rheumatoid arthritis), immunodeficiency disorders (e.g., HIV), and recurrent pulmonary infections (e.g., pneumonia).[2] Additionally, NCFB often coexists with other pulmonary conditions, such as chronic obstructive pulmonary disease (COPD), which are associated with poor outcomes.

The estimated prevalence of NCFB in the United States ranges from 230,000 and 430,000 cases, with increasing incidence rates annually.[3,c] The clinical presentation of NCFB typically include chronic productive cough with sputum production, recurrent airway infections, and frequent exacerbations. The progressive decline in lung function caused by NCFB can lead to frequent hospitalizations and a significant impact on a patient's quality of life. Furthermore, the all-cause mortality in the US ranges from 11-20% in the first 6 years following diagnosis.[4,d]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

3.2. Description of Current Treatment Options

There are currently no FDA-approved medications for the treatment of NCFB, representing an unmet medical need. Available treatment options aim to manage patient symptoms, reduce infections and exacerbations, and improve patients' quality of life. Treatment options may include oral and intravenous antibiotics for treating acute infections and exacerbations.[2] For patients with frequent exacerbations or for those with chronic airways infections, long-term oral or inhaled antibiotics (e.g., macrolides) can be considered. However, prolonged use is associated with antibiotic resistance.[5] Mucolytics and inhaled hypertonic saline may also be used in the treatment of NCFB to enhance mucociliary clearance.[2] For severe cases of NCFB and end-stage lung disease, lung resection or lung transplantation may also be considered.[6]

4. Benefit Assessment

The efficacy of brensocatib was established by two adequate and well-controlled trials, Study 301 (NCT04594369) and Study 201 (NCT03218917). Both trials were randomized, double-blind, placebo controlled, parallel-group, multicenter, multinational clinical trials. In both trials, all adult subjects had a history of confirmed NCFB by chest computed tomography with at least two documented pulmonary exacerbations prior to screening in the past 12 months. In Study 301, adolescent pediatric subjects 12 years of age and older had at least one pulmonary exacerbation in the prior 12 months.[1]

Study 301 was a 52-week trial that included 1,721 adult and pediatric subjects 12 years of age and older with NCFB (1680 adults and 41 pediatric patients 12 years of age to less than 18 years of age) who were randomized to brensocatib 10 mg (n=583), brensocatib 25 mg (n=575), or placebo (n=563) administered orally once daily. The primary efficacy endpoint was the annualized rate of pulmonary exacerbations over the 52-week treatment period. Pulmonary exacerbations were defined as worsening of 3 or more of the following major symptoms over 48 hours: increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness, decreased exercise tolerance, fatigue and/or malaise, and hemoptysis resulting in a healthcare provider decision to prescribe systemic antibiotics. Pulmonary exacerbations were considered severe if requiring treatment with intravenous antibacterial drugs and/or resulted in hospitalization. Key secondary endpoints included time to first pulmonary exacerbations, proportion of subjects that were pulmonary exacerbation free at week 52, annualized rate of severe pulmonary exacerbation, and change in postbronchodilator forced expiratory volume in 1 second (FEV_1) at week 52. The efficacy results for Study 301 are summarized in Table 1.[1]

Study 201 was a 24-week trial that included 256 adult subjects with NCFB who were randomized to brensocatib 10 mg (n=82), brensocatib 25 mg (n=87), or placebo (n=87) administered orally once daily. The primary efficacy endpoint was the time to first pulmonary exacerbation over the 24-week treatment period. The time to first pulmonary exacerbation was longer for subjects receiving 10 mg and 25 mg compared to placebo. (hazard ratio of brensocatib 10 mg and 25 mg versus placebo; 0.58 and 0.62, respectively; 95% CI: 0.35 to 0.95 and 0.38 to 0.99, respectively).[1] This demonstrated statistically significant improvements with both doses in the primary endpoint.

Table 1: Primary and Key Secondary Efficacy Analyses of Pulmonary Exacerbations and FEV_1 Over 52 Weeks in Study 301[1]

	Placebo (N=563)	Brensocatib 10 mg (N=583)	Brensocatib 25 mg (N=575)
Annualized rate of PEx	1.29	1.02	1.04
Rate Ratio (95% CI)	--	0.79 (0.68,0.92)	0.81 (0.69,0.94)
Median Time to First PEx (weeks)	36.71	49.00	50.71
Hazard Ratio (95% CI)	--	0.81 (0.70,0.95)	0.83 (0.70,0.97)
Proportion of Patients that were PEx Free at Week 52 (%)	40.3	48.5	48.5
Odds Ratio (95% CI)	--	1.41 (1.11,1.81)	1.40 (1.10,1.79)
Annualized Rate of Severe PEx	0.19	0.14	0.14
Rate Ratio (95% CI)	--	0.74 (0.51,1.09)	0.74 (0.52,1.06)
LS Mean Change from Baseline in Post-bronchodilator FEV_1 (mL) at Week 52	-62	-50	-24
Difference vs Placebo (95% CI)	--	11 (-14,37)	38 (11,65)
Abbreviations: FEV_1, forced expiratory volume in 1 second; LS, least squares; PEx, pulmonary exacerbation			

The clinical review team concluded that the efficacy results from Study 301 and Study 201 support the benefit of brensocatib 10 mg and 25 mg for the treatment the treatment of NCFB in adult and pediatric patients 12 years of age and older.[e] Refer to the FDA Multidisciplinary Review and Evaluation: NDA 217673 Brinsupri (brensocatib) for more information.[7]

5. Risk Assessment & Safe-Use Conditions

The safety review of brensocatib relies on the clinical data from Study 301 and Study 201. The safety analysis was conducted and presented separately for each trial given the differences in the length of the treatment periods (52 weeks vs. 24 weeks) and in some key aspects of the enrolled populations (e.g., exclusion of certain etiologies of bronchiectasis from Study 201).[7]

In Study 301, 1,719 subjects received at least one dose of brensocatib or placebo, and a total of 1,156 subjects received at least one dose of brensocatib 10 mg or 25 mg orally once daily. A total of 306

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

(17.8%) subjects experienced at least one serious adverse event (SAE) in Study 301. The placebo group demonstrated a greater proportion of subjects with any SAEs (19.2%) compared to brensocatib treatment groups (17.4% for brensocatib 10 mg and 16.9% for brensocatib 25 mg). The most common SAEs reported were bronchiectasis, pneumonia, and COVID-19. There were 14 deaths reported in Study 301, seven of which received brensocatib (three in the 10 mg dose group and four in the 25 mg dose group). Among the seven deaths that received brensocatib, four were attributable to bronchiectasis or NCFB sequelae. None of the deaths were considered related to brensocatib. Adverse events leading to treatment discontinuation were infrequent and balanced across treatment groups (4.3% in the brensocatib 10 mg group, 3.8% in the brensocatib 25 mg group, and 4.1% in the placebo group).

In Study 201, 255 subjects received brensocatib or placebo, which consisted of 170 subjects treated with at least one dose of brensocatib 10 mg or 25 mg orally once daily. The safety profile for Study 201 was similar to Study 301; however, there was a higher incidence of gingival and periodontal adverse reactions observed in Study 201. A total of 40 (15.7%) subjects experienced at least one SAE, with the greatest proportion of SAEs occurring in the placebo group. Adverse events leading to treatment discontinuation were also greater in the placebo group. There was one death reported in Study 201 in a 67-year-old subject that received brensocatib 25 mg. The death was deemed related to the progression of underlying bronchiectasis.

The Warnings and Precautions section of the proposed labeling will describe the risk of dermatologic adverse reactions, gingival and periodontal adverse reactions, and live attenuated vaccines.[f] At the time of this review, labeling negotiations were still ongoing with the Applicant.

5.1. Dermatologic Adverse Reactions

Treatment with brensocatib is associated with an increase in dermatologic adverse reactions, including rash, dry skin, and hyperkeratosis.[1] These events were generally mild and rarely resulted in treatment discontinuation; however, referral to dermatologist for treatment was indicated for most subjects who developed new skin findings.[7]

The Warnings and Precautions section of the proposed label advises healthcare providers to monitor patients for development of new rashes or skin conditions and refer patients to a dermatologist for evaluation of new dermatologic findings.

5.2. Gingival and Periodontal Adverse Reactions

The incidence of gingival and periodontal adverse reactions among subjects treated with brensocatib 10 mg and 25 mg in Study 201 were 9.9% and 10.1%, respectively, compared to 2.4% in placebo-treated subjects. The Warnings and Precautions section of the proposed label advises healthcare providers to

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

refer patients to dental care services for regular dental checkups while taking brensocatib, and to advise patients to perform routine dental hygiene.

5.3. Live Attenuated Vaccines

The concomitant use of brensocatib and live attenuated vaccines has not been evaluated. It is unknown whether administration of live attenuated vaccines during brensocatib treatment will affect the safety or effectiveness of these vaccines. The Warnings and Precautions of the proposed label advises healthcare providers that the use of live attenuated vaccines should be avoided in patients receiving brensocatib.

6. Expected Postmarket Use

Brensocatib is expected to be primarily prescribed in both inpatient and outpatient settings. The expected prescribers of brensocatib are pulmonologists who are expected to be able to monitor and educate patients on the risks and refer patients to dermatologists or dentists as needed. Brensocatib will be self-administered by the patient or caregiver.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for brensocatib beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical review team recommends approval of brensocatib on the basis of the efficacy and safety information currently available. Brensocatib will be indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older. NCFB is a chronic lung condition involving chronic productive cough with sputum production, recurrent airway infections, and frequent exacerbations requiring hospitalizations. There are currently no FDA-approved medications for the treatment of NCFB, representing an unmet medical need.

The risks associated with brensocatib are dermatologic adverse reactions, gingival and periodontal adverse reactions, and live attenuated vaccines. The benefit-risk profile is favorable, and the risks will be communicated in the Warnings and Precautions section of labeling. The proposed label advises healthcare providers to monitor patients for the development of new rashes or skin conditions and refer patients to a dermatologist for evaluation of new dermatologic findings. Additionally, the proposed label advises healthcare providers to avoid use of live attenuated vaccines with brensocatib and to refer patients to dental care services for regular dental checkups while taking brensocatib. The expected prescribers of brensocatib are pulmonologists who are expected to be able to monitor and educate patients on these risks and refer patients to dermatologists or dentists as needed. Based on the available efficacy and safety information, DRM and DPACC have determined that a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for brensocatib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

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