SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Brinsupri 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg of brensocatib (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Grey, approximately 9 mm diameter round tablet debossed with “25” on one side and “BRE” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Brinsupri is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in patients 12 years of age and older with two or more exacerbations in the prior 12 months.

4.2 Posology and method of administration

Posology

The recommended dose is 25 mg orally once daily with or without food.

Missed dose

Patients who miss a dose should take the next dose at their regular time the next day. Patients should not double the dose to make up for the missed dose.

Special populations

Elderly

No dose adjustment is required for elderly patients (see section 5.2).

Renal and hepatic impairment

No dose adjustment is required for patients with renal or hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Brinsupri in children younger than 12 years of age have not yet been established. No data are available.

Method of administration

For oral use.

This medicinal product should be taken once daily with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Immunocompromised patients

Safety data in patients with known or suspected immunodeficiencies, immunocompromised conditions, or receiving any immunomodulatory therapy are limited or not established. Administration of brensocatib in these patients should be considered with caution. Caution is advised when using brensocatib in patients with moderate to severe neutropenia (absolute neutrophil count [ANC] < 1,000/mm^3).

Vaccinations

The concomitant use of brensocatib and live attenuated vaccines has not been evaluated. The use of live attenuated vaccines should be avoided in patients receiving brensocatib.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies are inconclusive regarding the potential of brensocatib to induce CYP2B6 and CYP3A4 (see section 5.2). *In vivo* induction cannot be excluded. Co-administration with CYP3A4 substrates used in bronchiectasis (e.g. inhaled corticosteroids, macrolide antibiotics or inhaled bronchodilators such as salmeterol or vilanterol) may result in decreased plasma concentrations and reduced therapeutic effect. Adjustment of the concomitant treatment may be considered if efficacy is reduced.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of brensocatib in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3).

Benefits and potential risks of use of brensocatib during pregnancy have not been established. Brensocatib may be used during pregnancy where the expected benefit to the mother justifies the unknown risk to the fetus.

Breast-feeding

It is unknown whether brensocatib or its metabolites are excreted in human milk. Available data in animals have suggested excretion of brensocatib in milk (see section 5.3).

The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known.

Decisions on whether to breastfeed during treatment or to abstain from brensocatib therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies indicate no impact on male or female fertility at the clinically relevant exposure in patients treated with brensocatib (see section 5.3).

4.7 Effects on ability to drive and use machines

Brinsupri has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are headache (9.2%), hyperkeratosis (5.9%), dermatitis (4.2%), rash (4.1%), upper respiratory tract infections (3.9%), and dry skin (3.0%).

Tabulated list of adverse reactions

The safety of brensocatib was evaluated on the pooled safety population from two placebo-controlled clinical trials, ASPEN and WILLOW, which consisted of 1 326 adult and 41 adolescent patients 12 years of age and older with NCFB who received at least one dose of brensocatib for up to 52 weeks.

The frequency of adverse reactions is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection Gastroenteritis
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Gingival disorder Periodontal disease

System organ class	Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	Common	Hyperkeratosis* Rash Dry skin Dermatitis Skin exfoliation Alopecia

* See 'Description of selected adverse reactions' below.

Description of selected adverse reactions

Hyperkeratosis

In the pooled safety population, hyperkeratosis (including skin lesion, keratosis pilaris, exfoliative rash and seborrheic keratosis) was reported more frequently with brensocatib 25 mg than placebo (5.9% vs 3.1%). All events were of mild or moderate severity. Most resolved with no action taken with study treatment. Most cases were manageable or improved/resolved with emollients or topical steroids.

Paediatric population

The safety assessment in adolescents aged 12 to 17 with NCFB is based on 41 subjects exposed to brensocatib in the 52-week Phase 3 ASPEN trial (see section 5.1). The safety profile in these adolescents was similar to that observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Doses of up to 120 mg, given as a single dose, did not have evidence of dose-related toxicities.

There is no specific treatment for an overdose with brensocatib. If an overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

Mechanism of action

Brensocatib is a competitive and reversible inhibitor of dipeptidyl peptidase 1 (DPP1). DPP1 activates pro-inflammatory neutrophil serine proteases (NSPs) during neutrophil maturation in the bone marrow. Brensocatib reduces the activity of NSPs implicated in the pathogenesis of bronchiectasis, including neutrophil elastase, cathepsin G and proteinase 3.

Pharmacodynamic effects

At 5 times the maximum recommended daily dose of brensocatib, there was no effect on QTc prolongation.

Clinical efficacy

The efficacy of brensocatib was assessed in a Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial (ASPEN) with a total of 1 721 patients 12 years of age and older with NCFB (1 680 adults and 41 adolescents).

All patients were randomised to one of two doses of brensocatib (25 mg: n = 575) or placebo (n = 563), administered once daily for 52 weeks.

All adult patients enrolled had a history of confirmed NCFB by chest computed tomography with at least 2 documented pulmonary exacerbations prior screening in the past 12 months. Adolescent patients had at least one pulmonary exacerbation in the prior 12 months. A qualifying exacerbation was defined by the need for a physician-prescribed course of systemic antibiotics for signs and symptoms of respiratory infection.

Demographics and baseline characteristics of ASPEN are provided in Table 2.

Table 2: Demographics and baseline characteristics of patients in ASPEN

	Brensocatib 25 mg (N = 575)	**Placebo (N = 563)**
Age (years), mean (SD)	61 (16)	60 (15)
Female n (%)	360 (63)	362 (64)
White n (%)	430 (75)	405 (72)
Black or African American n (%)	5 (1)	3 (1)
Asian n (%)	64 (11)	64 (11)
Hispanic or Latino n (%)	164 (29)	170 (30)
≥ 3 PEx in prior 12 months n (%)	163 (28)	167 (30)

	Brensocatib 25 mg (N = 575)	**Placebo (N = 563)**
Former smoker n (%)	163 (28)	183 (33)
$ppFEV_1$ post-bronchodilator, mean (SD)	74 (25)	72 (22)
Sputum positive for *Pseudomonas aeruginosa* n (%)	205 (36)	199 (35)
Chronic macrolide therapy n (%)	114 (20)	105 (19)
QOL-B Respiratory Symptoms Domain Score, mean (SD)*	62 (17)	60 (17)

*adults only

N = number of patients in the intent-to-treat analysis set; n = number of patients; PEx = pulmonary exacerbations; pp = percent predicted; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation

Exacerbations

The primary efficacy endpoint in ASPEN was the annualised rate of pulmonary exacerbations (PEx) over the 52-week treatment period.

Pulmonary exacerbations were defined as worsening of 3 or more major symptoms over 48 hours with increase in cough, sputum volume, sputum purulence or increased breathlessness or decreased exercise tolerance and fatigue and/or malaise and, haemoptysis, resulting in a healthcare provider's decision to prescribe systemic antibiotics. Pulmonary exacerbations were considered as severe if requiring treatment with intravenous antibiotics and/or resulted in hospitalisation.

In ASPEN, treatment with Brinsupri 25 mg in patients with NCFB demonstrated significant reductions in the annualised rate of pulmonary exacerbations compared with placebo (Figure 1). Key results are shown in Table 3.

The time to first pulmonary exacerbation was significantly longer for patients receiving Brinsupri 25 mg compared with placebo in ASPEN (Figure 2). Treatment with Brinsupri 25 mg significantly increased the proportion of patients remaining exacerbation free throughout the 52-week treatment period. There were fewer severe exacerbations with Brinsupri 25 mg.

Table 3: Exacerbations endpoints over 52 weeks in ASPEN

	Brensocatib 25 mg (N = 575)	**Placebo (N = 563)**	
Annualised rate of PEx	1.04	1.29	Rate ratio (95% CI): 0.81 (0.69, 0.94)
Median time to first PEx (weeks)	50.71	36.71	Hazard ratio (95% CI): 0.83 (0.70, 0.97)
Proportion of patients that were exacerbation free at week 52 (%)	48.5	40.3	Odds ratio (95% CI): 1.40 (1.10, 1.79)
Annualized rate of severe PEx	0.14	0.19	Rate ratio (95% CI): 0.74 (0.52, 1.06)

Figure 1: **Cumulative number of pulmonary exacerbations through week 52**

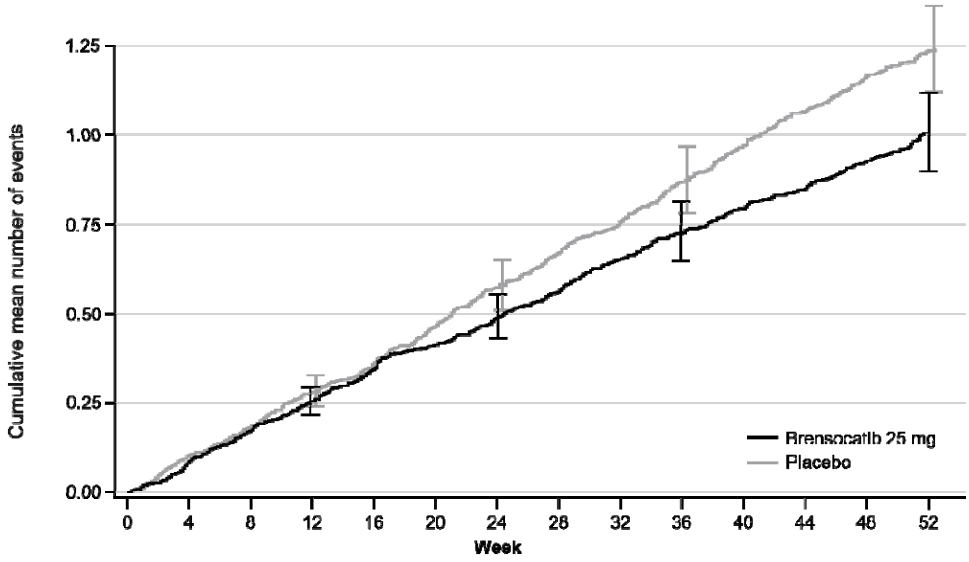
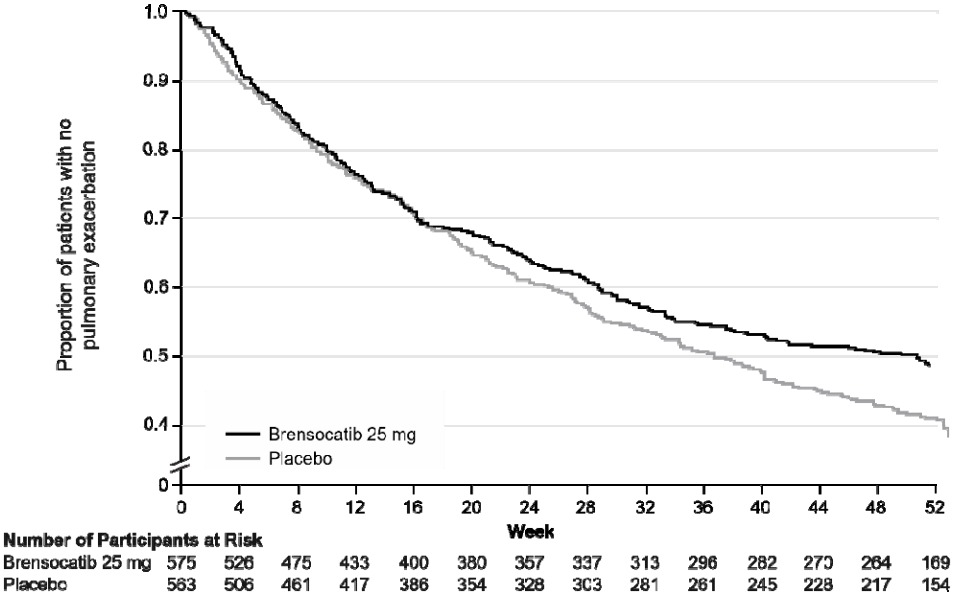


Figure 2: **Kaplan-Meier curve for time to first pulmonary exacerbation**



Lung function

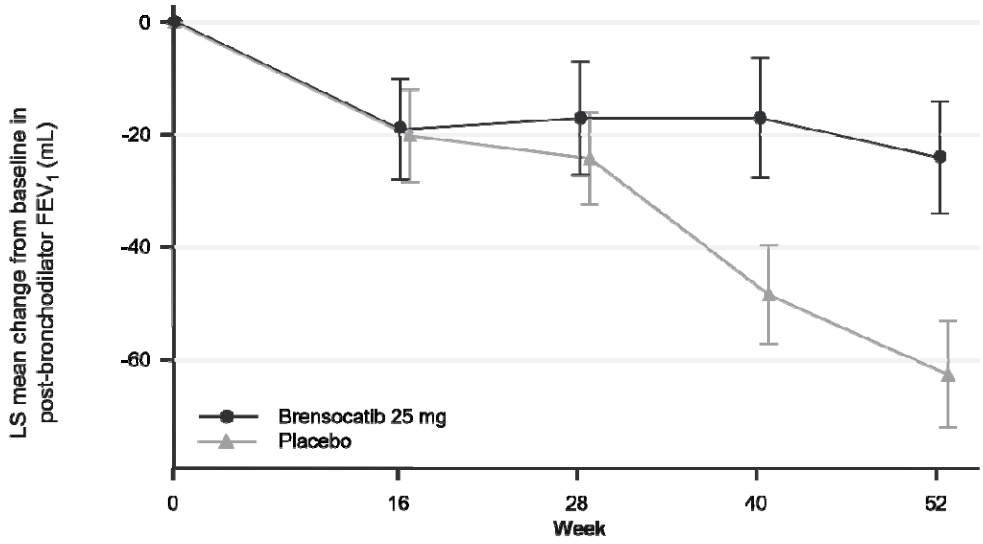
Change from baseline in post-bronchodilator FEV_1 was assessed as a secondary endpoint. Brinsupri 25 mg significantly reduced FEV_1 decline in comparison to placebo at week 52 (Table 4, Figure 3).

Table 4: **Change from baseline in post-bronchodilator FEV1 (mL) at week 52**

	Brensocatib 25 mg (n=575)	Placebo (n=563)	Difference vs Placebo (95% CI)
LS Mean Change from Baseline	-24	-62	38 (11, 65)

LS = Least Squares

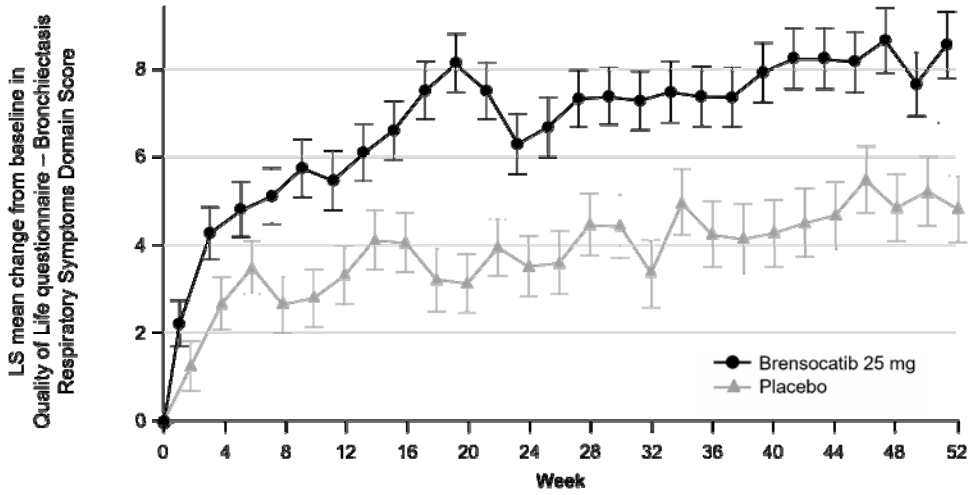
Figure 3: LS mean change (SE) from baseline in post-bronchodilator FEV1 (mL) over time



Patient reported outcomes

Change from baseline in the Quality-of-Life Bronchiectasis Respiratory Symptoms Domain Score (QOL-B RSS) was assessed every 2 weeks throughout the study. A higher QOL-B RSS represents fewer respiratory symptoms; a positive change from baseline indicates improvement of respiratory symptomatology. The LS mean change from baseline at week 52 for Brinsupri 25 mg was 8.58 versus 4.81 in the placebo group (LS mean difference 3.77; 95% CI: 1.68, 5.85) (Figure 4).

Figure 4: LS mean change (SE) from baseline in QOL-B Respiratory Symptoms Domain Score over time



Paediatric population (adolescents)

In the pivotal 52-week study, 41 adolescents (12 to < 18 years) were randomised to brensocatib 25 mg once daily, brensocatib 10 mg once daily or placebo. The adolescent subgroup was small and the study was not powered for efficacy in adolescents; confidence intervals were wide and results are inconclusive. Trends towards fewer pulmonary exacerbations and positive changes in post-bronchodilator FEV_1 were observed with 25 mg brensocatib versus placebo. Safety and pharmacokinetic data in adolescents were generally consistent with adults (see sections 4.8 and 5.2).

The MHRA has waived the obligation to submit the results of studies with Brinsupri in children from birth to less than 6 years in treatment of NCFB (see section 4.2 for information on paediatric use).

The MHRA has deferred the obligation to submit the results of studies with Brinsupri in one or more subsets of the paediatric population in NCFB (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of brensocatib has not been studied in humans. Brensocatib is rapidly absorbed after oral administration. T_{max} for tablets is approximately 1 hour in patients. Brensocatib oral absorption is not affected by food intake. Co-administration with a high fat meal delayed the time to reach peak concentration by 0.75 hours, however, the extent of brensocatib absorption remained the same.

Distribution

After oral administration, the volume of distribution at steady state was 126-138 L (CV: 22.4-23.3%) in adult patients and 71.3-83.6 L (CV: 19.9-26.3%) in adolescents with NCFB. The protein binding of brensocatib to human plasma was 82.2-87.2%.

Biotransformation

Brensocatib undergoes metabolism primarily by CYP3A. Brensocatib accounted for 16.2% of the total radioactivity in plasma. Only one major circulating metabolite, thiocyanate, was detected in plasma. Thiocyanate is an endogenous compound, and clinical data showed that thiocyanate plasma concentrations were not affected and remained in the normal range on brensocatib treatment.

Interactions

In vitro studies

CYP450 enzymes

Brensocatib is a substrate of CYP3A.

Brensocatib does not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. *In vitro* studies are inconclusive regarding the potential of brensocatib to induce CYP2B6 and CYP3A4. *In vivo* induction cannot be excluded.

Transporter systems

Brensocatib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Brensocatib is not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2.

Brensocatib is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

Effect of brensocatib on other medicinal products

In vitro data and population pharmacokinetic analyses indicate that brensocatib is unlikely to inhibit or significantly induce the activity of CYP isozymes or drug transporters at clinically relevant dose levels. However, *in vitro* studies were inconclusive regarding the potential of brensocatib to induce CYP2B6 and CYP3A4, and *in vivo* induction cannot be excluded.

Effect of other medicinal products on brensocatib

Brensocatib AUC and C_{max} increased by 55% and 68% with a strong CYP3A inhibitor (e.g. clarithromycin) and by 32% and 53% with a strong P-gp inhibitor (e.g. verapamil) but decreased by 33% and 15% with a strong CYP3A inducer (e.g. rifampicin). C_{max} and AUC remained unchanged with a potent proton-pump inhibitor (e.g. esomeprazole). The interaction effect on brensocatib systemic exposure is not clinically meaningful.

Elimination

Following a single oral dose of radiolabelled brensocatib, 54.2% of dose was excreted in urine and 28.3% in faeces with most radioactivity excreted within 72 hours. The unchanged brensocatib in urine and faeces were 22.8% and 2.41% of dose, respectively.

Terminal half-life was 32.6-39.6 hours (CV: 26.6-33.0%) in adult patients and 26.9-27.8 hours (CV: 26.8-37.3%) in adolescent patients.

Linearity/non-linearity

Brensocatib exhibits linear and time-independent pharmacokinetics with low to moderate intra- and inter-subject variability over a dose range of 5-120 mg following single administration and a dose range of 10-40 mg following once-daily administration. Population pharmacokinetics analysis using pooled data from 11 clinical studies in healthy subjects (n = 291) and patients with NCFB (n = 783) showed that brensocatib pharmacokinetics can be adequately described by a 2-disposition compartments with first-order oral absorption.

Pharmacokinetic/pharmacodynamic relationships

Exposure-response relationships were observed between brensocatib exposure (AUC) and clinical efficacy (i.e. decline of lung function measured as FEV_1). At 25 mg, > 99% NCFB patients in the ASPEN trial achieved an AUC threshold that was associated with clinically meaningful improvement in FEV_1. No exposure-response relationships were detected for the occurrence of periodontal disease or pneumonia. A relationship between brensocatib exposure (AUC) and hyperkeratosis (mild and moderate) was observed. However, the predicted probability of mild or moderate hyperkeratosis was low at brensocatib 25 mg (3.01% in adults and 3.36% in adolescents).

Special populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (range: 12 to 85 years), sex, race/ethnicity, or body weight (range: 32 to 155 kg) on the pharmacokinetics of brensocatib.

Paediatric population

Based on the population pharmacokinetic analysis, there was no clinically meaningful age-related difference in the pharmacokinetics of brensocatib between adults and adolescents aged 12 to 17 years. Brensocatib has not been studied in children under 12 years of age (see section 4.2).

Hepatic impairment

In subjects with mild, moderate or severe hepatic impairment (Child-Pugh scores 5 to 12), brensocatib clearance following a single dose was comparable to that in healthy subjects. No dose adjustments are recommended for patients with mild, moderate or severe hepatic impairment (see section 4.2).

Renal impairment

In subjects with mild, moderate or severe renal impairment, (creatinine clearance ≥ 15 mL/min/1.73 m^2 and not requiring dialysis), brensocatib clearance following a single dose was comparable to that in healthy subjects. No dose adjustments are recommended for patients with mild, moderate or severe renal impairment (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

General toxicity

In a 6-month rat study microscopic changes in the kidney (basophilic tubules in the outer medulla) and the lung (perivascular neutrophil infiltration and vacuolated macrophage accumulation consistent with phospholipids) were observed at 50 mg/kg/day. The no-observed-adverse-effect-level was considered to be 9 mg/kg/day (AUC 20 times the maximum recommended human dose [MRHD]).

In a 9-month dog study no adverse findings were observed at any dose (AUC 5 times the MRHD). In a preceding 6-month dog study, administration of brensocatib at 50 mg/kg/day caused periodontal disease resulting in early termination of the group. At ≥ 8 mg/kg/day, dose-dependent microscopic findings were noted in the testis (seminiferous tubule degeneration and atrophy), in the epididymis (decreased number of spermatozoa and cellular debris), and in the lung (accumulations of vacuolated macrophages consistent with phospholipids). At 50 mg/kg/day, additional microscopic findings were noted in the kidney (tubular regeneration) and in the lymphoid tissues (axillary, mandibular and mesenteric lymph nodes, gut associated lymphoid tissue and spleen) as indicated by the accumulations of vacuolated macrophages.

Reproductive and developmental toxicity

In a rat fertility and embryo-foetal development study, following treatment with brensocatib from 2 weeks prior to mating, during mating and up to the end of major embryonic organogenesis, recoverable minor malformations of bent scapula and wavy ribs were noted at plasma exposure (AUC) 128-times the human exposure at the MRHD. There was an increased incidence of skeletal variations (malpositioned pelvic girdle and vestigial supernumerary full and/or short ribs in both cervical and thoracolumbar regions) and differences in ossification at AUC ≥ 42-times the human exposure at the MRHD. The no effect dose for developmental toxicity was at AUC of 3-times the human exposure at the MRHD. In a rabbit embryo-foetal development study, once-daily oral administration of brensocatib to pregnant rabbits from gestation day 7 to 19 at 15 or 50 mg/kg/day caused slight maternal toxicity indicated by a slight reduction in body weight gain and some transient reductions in food consumption at 50 mg/kg/day only. The no observed adverse effect level for maternal toxicity was

considered to be 5 mg/kg/day (AUC 2 times the MRHD). There was no effect on embryofoetal survival or foetal development in rabbits at any dose level.

In a pre- and post-natal development study in rats treated from gestation day 6 through lactation day 20, no adverse findings were observed at any dose (up to AUC 17-times the human exposure at the MRHD). Brensocatib was detected in pups, suggesting that male and female pups were likely exposed via maternal milk during lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline

Calcium hydrogen phosphate dihydrate

Sodium starch glycolate

Silica, colloidal hydrated

Glycerol dibehenate

Film-coating

Poly(vinyl alcohol)

Titanium dioxide

Macrogol

Talc

Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PCTFE aluminium foil blister card containing 14 film-coated tablets.

Pack size of 28 tablets (2 blister cards of 14 tablets each) in a carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Insmed Netherlands B.V.

Stadsplateau 7

3521 AZ Utrecht

Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 47434/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/02/2026

10 DATE OF REVISION OF THE TEXT

20/02/2026