EU RISK MANAGEMENT PLAN (RMP) FOR

Gefapixant Tablet

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

The following terms may be used interchangeably within the document:

Participant and subject

Study and trial

Intervention and treatment

Sex and gender

ACE	Angiotensin-converting Enzyme
ADR	Adverse Drug Reaction
AHI	Apnea/Hypopnea Index
ATC	Anatomical Therapeutic Chemical classification system
BID	Twice A Day
CHEST	The American College of Chest Physicians
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
DPI	Dry pressurized inhalers
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERS	European Respiratory Society
ESRD	End-stage renal disease
EU	European Union
FDA	Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
ICS	Inhaled Corticosteroids
INN	International Nonproprietary Name
LCQ	Leicester Cough Questionnaire
MAH	Marketing Authorization Holder
N/A	Not Applicable
OSA	Obstructive Sleep Apnea

NAEB	Non-Asthmatic Eosinophilic Bronchitis
PAES	Post-authorization Efficacy Study
PAP	Positive airway pressure
pMDI	Pressurized Metered-Dose Inhalers
PSUR	Periodic Safety Update Report
PT	Preferred Term
QHS	Daily at bedtime
QPPV	Qualified Person for Pharmacovigilance
RCC	Refractory Chronic Cough
RMP	Risk Management Plan
SaO_2	Oxygen saturation
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitors
UACS	Upper Airway Cough Syndrome
UCC	Unexplained Chronic Cough

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

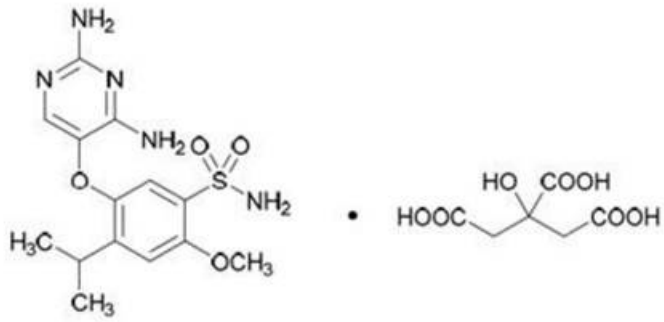
Active substances (INN or Generic name)	Gefapixant
Pharmacotherapeutic group(s) (ATC Code)	Not available yet
Marketing Authorisation Holder	Merck Sharp & Dohme B.V.
Number of medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Lyfnua®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Gefapixant is an orally-active selective antagonist of the P2X3 receptor. The designation MK-7264 refers to the active free base that is delivered in the formulation as the citrate salt. The chemical name for gefapixant citrate salt is 5-[(2,4-Diamino-5-pyrimidinyl)oxy]-2-methoxy-4-(1-methylethyl)benzenesulfonamide. Gefapixant citrate salt has a molecular formula of $C_{14}H_{19}N_5O_4S \cdot C_6H_8O_7$ and a molecular weight of 545.52. Structure: 
	Summary of mode of action Gefapixant is a selective antagonist of the P2X3 receptor. Gefapixant also has activity against the P2X2/3 receptor subtype. P2X3 receptors are ATP-gated ion channels found on sensory C fibers of the vagus nerve in the airways. C fibers are activated in response to inflammation or chemical irritants. ATP is released from airway mucosal cells under conditions of inflammation. Binding of extracellular ATP to P2X3 receptors is sensed as a damage signal by C fibers. Activation of C fibers, which is sensed by the patient as an urge to cough, initiates a cough reflex. Blockade of extracellular ATP signaling through P2X3 receptors reduces sensory-nerve activation and cough.
	Important information about its composition Gefapixant is available as 45 mg film-coated tablets Active Ingredient Each film-coated tablet contains 45 mg of gefapixant (as gefapixant citrate) Inactive Ingredients (List of excipients)

Table I.1: Product Overview

	Tablets of gefapixant contain the following inactive ingredients: colloidal anhydrous silica, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, sodium stearyl fumarate. The film coating contains iron oxide red, hypromellose, titanium dioxide, and triacetin. The coated tablets are polished with carnauba wax.
Hyperlink to the Prescribing Information	See proposed Prescribing Information in Module 1.3
Indications in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): Gefapixant is indicated in adults for the treatment of refractory or unexplained chronic cough
Dosage in the EEA	Current (if applicable): One 45 mg tablet taken orally twice daily with or without food
	Proposed (if applicable): Not applicable
Pharmaceutical forms and strengths	Current (if applicable): 45 mg film- coated tablet
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Chronic cough

Worldwide, chronic cough is a common medical condition in adults; this condition prompts patients to seek a healthcare consultation that in turn may lead to referrals to respiratory specialists (including pulmonologists or allergists). The importance of cough as a clinical problem has led to multiple scientific societies publishing guidelines on the diagnosis and management of cough [Ref. 5.4: 04KQPD, 04KW7B, 03QMXM, 04KW9M, 04KQP6, 05LJTX]. In these clinical guidelines, cough is categorized based upon duration. Cough in adults can be classified as acute (<3 weeks), subacute (3 to 8 weeks), or chronic (>8 weeks).

Clinical guidelines [Ref. 5.4: 04N3R4, 0528XS] recommend that patients with chronic cough be evaluated for potentially treatable causes, including malignancy, infection, drugs known to cause cough, smoking or comorbid diseases known to be associated with chronic cough (e.g., asthma, gastroesophageal reflux disease (GERD), upper airway cough syndrome (UACS), or non-asthmatic eosinophilic bronchitis (NAEB)) [Ref. 5.4: 04N3R4]. The majority of patients with chronic cough associated with an underlying condition respond to treatment for the comorbid condition; however, in a subset of patients, the cough is either refractory to treatment of the associated condition or no associated condition can be identified. Patients who have been diagnosed with conditions that are suspected to cause chronic cough, but whose cough does not resolve with the appropriate treatment are considered to have refractory chronic cough (RCC). Patients with chronic cough in whom an underlying etiology cannot be identified despite a thorough diagnostic workup are considered to have unexplained chronic cough (UCC).

Incidence:

The epidemiology of chronic cough is not well defined. Studies documenting the incidence of chronic cough are rare. A recent study estimated the incidence of chronic cough, using information collected as part of the Rotterdam Study, an ongoing prospective population-based cohort study that investigates the occurrence and determinants of chronic diseases among participants aged ≥45 years in the Netherlands [Ref. 5.4: 05KGRG]. Chronic cough was assessed using standardized questionnaires and defined as daily coughing for at least 3 months duration during the preceding 2 years [Ref. 5.4: 05KGRG]. During an average follow-up of 6 years, 439 incident cases of chronic cough occurred with an overall incidence rate of 11.6 per 1000 person-years (95% CI 10.6–12.8) [Ref. 5.4: 05KGRG].

Prevalence:

Observational studies estimating the prevalence of chronic cough lack consistent validated epidemiologic definitions of chronic cough. In a global meta-analysis of 90 studies, utilizing studies with different definitions of chronic cough, the overall prevalence of chronic cough in the general adult population was 9.6% (95% confidence interval (CI), 7.6-11.7); the highest rates of chronic cough were reported in Oceania (18.1%; 95% CI, 9.8-27.2), Europe (12.7%;

95% CI, 10.4-15.2), and the United States (11.0%; 95% CI, 7.8-14.4), with lower rates reported in Asia (4.4%; 95% CI, 1.8-7.4) and Africa (2.3%; 95% CI, 0.0-6.7) [Ref. 5.4: 04MLZM]. A study in southeast England of 9,077 patients reported a 12% prevalence of chronic cough, where chronic cough was defined as coughing at least half of the days of the year in patients 5 years of age or older[Ref. 5.4: 03QMXR]. A study in Italy of 18,000 people 20-44 years of age reported a 11.9% prevalence of chronic cough, where chronic cough was defined as having cough or phlegm on most days for at least 3 months of the year and for at least two successive years [Ref. 5.4: 05F889]. Of the 9,824 participants in the Rotterdam study, 10.9% of participants had chronic cough at baseline, where chronic cough was defined as minimum 3 months duration of cough during the preceding 2 years [Ref. 5.4: 05KGRG]. An estimated 2% of the Japanese population ages 10 years and older may suffer from chronic cough, defined as cough lasting ≥ 8 weeks [Ref. 5.4: 04W32Z].

Chronic cough has been estimated to affect up to approximately 12% of the adult population recruited from primary care clinics in Europe, although there are prevalence estimates as low as 4% [Ref. 5.4: 03QMXS, 05FNJS, 05KGRG]. More recently, Kantar Health conducted the 2018 National Health and Wellness Survey in five European countries, including France, Germany, Italy, Spain and the United Kingdom [Ref. 5.4: 05GR0C]. (Henceforth, referred to as the 2018 European National Health and Wellness Survey). In this survey, approximately 5% of adults in each of these European countries self-reported experiencing chronic cough in the past 12 months and about 2% were diagnosed with chronic cough by a physician. In this cross-sectional survey chronic cough was defined as having a daily cough for at least eight weeks [Ref. 5.4: 05GR0C].

Demographics of the population in the chronic cough indication:

In a retrospective review of unselected patient referrals to 11 specialist cough clinics from Europe, North America and Asia, patients with persistent cough without significant radiological abnormality, were selected [Ref. 5.4: 05278V]. A total of 10,032 patients were seen in the clinics from November 2003 to March 2013 [Ref. 5.4: 05278V]. Two-thirds of the patients (n=56,591, 66%) attending the clinics were women [Ref. 5.4: 05278V]. The mean age ± standard deviation (SD) was 55 ± 14.97 years. The most common age for presentation was 60–69 years [Ref. 5.4: 05278V]. Similarly, in the 2018 European National Health and Wellness Survey, 63% of respondents self-reporting chronic cough were women and the mean age of respondents self-reporting chronic cough was 55 years [Ref. 5.4: 05GR0C]. In the 2018 National Health and Wellness Survey sample in the United States the one-year prevalence of chronic cough was 5.0%. In this sample, the prevalence of chronic cough in the previous 12 months (n=3,654) was higher among females than males (60.4% vs 39.6%), and those aged 50 years or older than aged 18-49 years (53.9% vs 46.1%) [Ref. 5.4: 05JKLF].

Risk factors for the disease:

Common causes of chronic cough include asthma, GERD, UACS, and NAEB [Ref. 5.4: 0528XS].

Patients who have been diagnosed with conditions that are suspected to cause chronic cough (i.e., asthma, GERD, UACS, or NAEB) [Ref. 5.4: 0528XS] but whose cough does not resolve with the appropriate treatment of those conditions are considered to have RCC [Ref. 5.4: 05284T]. A retrospective United Kingdom study examining the etiology of chronic cough reported that treatment of the suspected cause was ineffective in resolving cough in 17% (17/100) of patients [Ref. 5.4: 052DDS]. Patients with chronic cough in whom an underlying etiology cannot be identified despite a thorough diagnostic workup are considered to have UCC [Ref. 5.4: 05284T]. A retrospective study conducted in the United Kingdom examining the etiology of chronic cough reported that an underlying cause could not be determined in 25% (25/100) of patients with chronic cough [Ref. 5.4: 052DDS].

Treatment options:

There are no medicinal products approved by the EMA or Food and Drug Administration (FDA)for the treatment of chronic cough, including RCC or UCC [Ref. 5.4: 052860]. In small randomized trials, the neuromodulating agents gabapentin and amitriptyline have demonstrated some benefit in patients with chronic cough [Ref. 5.4: 04Q6WR, 052D08], however, neither agent is approved for the treatment of cough [Ref. 5.4: 03RJ63, 052CWZ] and both are associated with considerable adverse drug reactions, such as nausea, dry mouth, sedation and fatigue [Ref. 5.4: 04Q6WR, 052D34]. A small randomized, double-blind, placebo-controlled study in patients with RCC (N=27) demonstrated that treatment with low-dose, slow-release morphine sulfate resulted in significant improvements in cough as assessed by the Leicester Cough Questionnaire (LCQ) and daily cough scores [Ref. 5.4: 05F5H7]. Constipation and drowsiness were common adverse effects reported in trial participants who received morphine. While the American College of Chest Physicians (CHEST) guidelines do not recommend the use of morphine for the treatment of UCC or RCC based on limited clinical evidence [Ref. 5.4: 04Q70K], the more recently published European Respiratory Society (ERS) guidelines strongly recommend a trial of low dose slow release morphine (5-10 mg twice a day) for adults with RCC [Ref. 5.4: 05HD4X].

A 2013 review by the Agency for Healthcare Research and Quality found that, of the agents identified in the literature, opioid and certain nonopioid/non-anesthetic antitussives were the treatments that most frequently demonstrated efficacy for managing the symptoms of chronic cough, although the inconsistency of results, lack of reliable outcome measures and low overall strength of evidence is insufficient to draw firm conclusions [Ref. 5.4: 05284T]. Morphine, codeine, and dextromethorphan have also been considered as potential cough therapies and carry safety and potential abuse concerns with chronic use [Ref. 5.4: 05284T].

Natural history of the indicated condition in the [untreated] population, including mortality and morbidity:

The burden of chronic cough (>8 weeks) is long lasting, with some patients experiencing persistent symptoms that may continue for years despite numerous healthcare provider visits, treatment trials, and medical tests. In a small double-blind, placebo-controlled, crossover trial evaluating patients taking low-dose morphine for RCC (N=22), the mean duration of cough at baseline was 14 years [Ref. 5.4: 0527Y8]. In a prospective, observational study of patients with chronic cough, 46% (31/68) of patients continued to report regular cough

5 years after the initial diagnosis and impairments in cough-related quality of life persisted in 47% (32/68) of patients [Ref. 5.4: 052CHH]. In a longitudinal study of patients with UCC or RCC who were followed for 7 to 10 years after diagnosis, the mean duration of cough was 11.5 years at the time of the final assessment, with 33% (14/42) reporting that their cough had worsened, 23% (10/42) that their cough was unchanged, 25% (11/42) that their cough had improved, and only 14% (6/42) reporting that their cough had resolved [Ref. 5.4: 052CTV].

Important comorbidities:

Common expected comorbidities and co-prescribed medicinal products

The incidence and prevalence of the comorbidities in the chronic cough, RCC, and UCC patient populations are not well studied and often based on small sample sizes. As a result, there is often a wide range of estimates.

The following are the best prevalence estimates of important common expected comorbidities for patients with chronic cough from the scientific literature and a listing of commonly co-prescribed medicinal products according to treatment guidelines for these co-morbidities. This list of co-prescribed medicinal products is not exhaustive.

Medical Conditions Associated with Chronic Cough

Asthma

In the prospective population-based Rotterdam study, 11.6% of the participants had asthma of the 1,073 participants in the Netherlands with chronic cough at baseline [Ref. 5.4: 05KGRG]. More recently, in a longitudinal observational study of 75 adults with chronic cough attending a cough specialty clinic in the United States, 27.5% had asthma at baseline[Ref. 5.4: 0528XQ]. In a retrospective study of 11,290 patients in the United States with specialist-diagnosed chronic cough, 31% of patients had asthma [Ref. 5.4: 05G7NR].

Co-prescribed medicinal products include: Controller medications: Inhaled corticosteroids ((ICS), pressurized metered-dose inhalers (pMDIs) or dry powder inhalers (DPIs)), inhaled corticosteroids and inhaled long-acting β-agonists bronchodilator combinations, leukotriene modifiers, and chromones (pMDIs or DPIs) [Ref. 5.4: 055QRD].

Add-on controller medications: Long-acting anticholinergic, anti-IgE, anti-IL5, systemic corticosteroids [Ref. 5.4: 055QRD].

Reliever medications: Short-acting inhaled β-agonists bronchodilator, low-dose ICS/formoterol, short-acting anticholinergics (pMDIs or DPIs) [Ref. 5.4: 055QRD].

Gastroesophageal reflux disease (GERD)

In the 2018 European National Health and Wellness Survey, 54% of self-reported chronic cough respondents reported having GERD, acid reflux or heartburn [Ref. 5.4: 05GR0C]. In a retrospective study of 11,290 patients in the United States with specialist-diagnosed chronic

cough 44% of patients experienced frequent GERD [Ref. 5.4: 05G7NR]. In the prospective population-based Rotterdam study, 18.3% of the 1, 073 participants in the Netherlands with chronic cough at baseline had GERD [Ref. 5.4: 05KGRG].

Co-prescribed medicinal products include: Antacids, proton pump inhibitors, H2 receptor antagonists, promotility drugs [Ref. 5.4: 05H90J].

Non-asthmatic eosinophilic bronchitis

In a longitudinal observational study of 75 adults with chronic cough attending a cough specialty clinic in the United States, 2.5% also had NAEB at baseline[Ref. 5.4: 0528XQ].

Co-prescribed medicinal products include: Inhaled corticosteroids, with add-on of a leukotriene inhibitor if not response to ICS [Ref. 5.4: 05H9QJ].

Upper airway cough syndrome

In retrospective study of 11,290 patients in the United States with specialist-diagnosed chronic cough, 20% had UACS [Ref. 5.4: 05G7NR]. More recently, in a longitudinal observational study of 75 adults with chronic cough attending a cough specialty clinic in the United States, 72.5% also had UACS at baseline[Ref. 5.4: 0528XQ].

Co-prescribed medicinal products include: Nasal application of H2-antihistamines, anticholinergic nasal spray First-generation antihistamines, decongestants [Ref. 5.4: 05HNZH].

Common Comorbidities in the Chronic Cough Population

Hypertension

In the 2018 European National Health and Wellness Survey countries, 38.3% of self-reported chronic cough patients reported having high blood pressure [Ref. 5.4: 05GR0C].

Co-prescribed medicinal products include: Antihypertensive medications (Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker, beta blocker, calcium channel blockers, and diuretics) [Ref. 5.4: 05H90L].

Sleep apnea and obstructive sleep apnea (OSA)

The 2018 National Health and Wellness Survey in the United States and the United Kingdom included respondents who self-reported having chronic cough, defined as having a daily cough for at least eight weeks. [Ref. 5.4: 05JKLF, 05JL5B]. In this survey, 16% (586/3654) of self-reported chronic cough patients in the United States and 10% (72/715) of self-reported chronic cough patients in the United Kingdom reported having sleep apnea [Ref. 5.4: 05JKLF, 05JL5B]. Smokers are included in these estimates. No information on Continuous Positive Airway Pressure (CPAP) treatment was collected.

In Taiwan, researchers conducted a retrospective cohort study of 131 patients who were referred to a sleep laboratory by thoracic physicians from January to June 2012. Of patients with OSA, 39% (39/99) had chronic cough, while only 12% (4/32) of patients without OSA had chronic cough. When OSA patients with chronic cough received CPAP, 67% (12/18) experienced a significant improvement in their chronic cough, whereas only 10% (2/21) of patients with OSA and chronic cough who did not receive CPAP experienced a significant improvement in their chronic cough [Ref. 5.4: 05MV3Z].

A retrospective review of records from a community-based pulmonary clinic in Utah from 2005 to 2009 documented the prevalence of OSA among patients with chronic cough/bronchitis (cough lasting for eight weeks or longer). Of the 75 chronic cough/bronchitis patients, 44% had any OSA, of whom 27% had moderate or severe OSA (with Apnea-Hypopnea Index >16) [Ref. 5.4: 05JCB0]. Improvement in cough was noted in 93% (25/27) of patients who had initiation of new CPAP therapy or re-titration to optimal CPAP pressures. Six patients were not treated with CPAP and resolution of their OSA is unknown[Ref. 5.4: 05JCB0].

A prospective cohort of 76 patients with UCC (cough lasting longer than 8 weeks, but also including smokers) who were referred to a specialty respiratory center at National Jewish Hospital, found that 58% of these patients had OSA [Ref. 5.4: 05JC9Z]. Information on treatment with CPAP was not provided.

OSA has been suggested as a potential risk factor for chronic cough. Further research is needed [Ref. 5.4: 05HD4X].

Potential Clinical Sequalae of Chronic Cough

Patients with RCC and UCC may experience substantial physical consequences, which may include stress urinary incontinence, sleep disturbance, breathlessness, chest pain, and, in some cases, severe effects such as cough-induced rib fracture or syncope [Ref. 5.4: 0528XV]. In a prospective study of patients attending a pulmonary specialty clinic in the United States with a complaint of chronic cough, 53% (72/136) of patients indicated that physical effects, including broken ribs, retching, chest pains, or hoarseness, were among the negative consequences of their cough [Ref. 5.4: 0528XV].

Depression/ worsening of depressive symptoms

Prevalence: In a survey administered to adults residing in Europe with chronic cough of any cause, 91% (1000/1120) of respondents indicated that they experienced frustration and depression and 81% (890/1120) of respondents reported that their cough affected activities that they enjoy [Ref. 5.4: 04MMTF]. In a US study examining symptoms of depression in patients with chronic cough, 53% (53/100) of evaluated patients had significant depressive symptomatology and risk of clinical depression at the time of treatment initiation; improvements in cough scores after 3 months correlated significantly with improvements in depression scores ($p=0.003$; Spearman $\rho = 0.323$) [Ref. 5.4: 04MMZ4].

In the 2018 European National Health and Wellness Survey, 35.6% of self-reported chronic cough patients reported experiencing depression [Ref. 5.4: 05GR0C].

Co-prescribed medicinal products include: Selective serotonin reuptake inhibitors (SSRIs), serotonin (5-hydroxytryptamine receptor) modulators (blockers), serotonin-norepinephrine reuptake inhibitors, dopamine-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, noradrenergic and specific serotonergic antidepressant, norepinephrine reuptake inhibitors, heterocyclic antidepressants (tricyclic antidepressants) [Ref. 5.4: 05H9QK].

Dizziness

In a United Kingdom community survey of individuals who requested information about chronic cough in response to a radio broadcast, 26% (95/373) of respondents reported that they experienced dizziness associated with their cough [Ref. 5.4: 0527YB].

Headache

The 2018 European National Health and Wellness Survey, 54.2% of self-reported chronic cough patients reported having headaches [Ref. 5.4: 05GR0C].

Loss of productivity

Prevalence: In a prospective study of patients attending a pulmonary specialty clinic in the United States with a complaint of chronic cough, 22% (30/136) of patients reported absenteeism from work or school, demonstrating that chronic cough negatively affects the ability to work. Furthermore, 63% (85/136) of patients reported interference with speaking and 66% (90/136) reported exhaustion or poor concentration [Ref. 5.4: 0528XV].

Sleep disturbance

Prevalence: In a prospective study of patients attending a pulmonary specialist clinic in the United States with a complaint of chronic cough, 79% (107/136) of patients reported that they experienced sleep disturbance associated with their cough [Ref. 5.4: 0528XV]. In the 2018 European National Health and Wellness Survey, 68.6% of self-reported chronic cough patients reported having a sleep condition, including sleep difficulties or insomnia [Ref. 5.4: 05GR0C].

Co-prescribed medications include: Sedatives, hypnotics including benzodiazepines, benzodiazepine receptor agonists, antidepressants, antipsychotics, antihistamines, phytotherapeutic substances and melatonin receptor agonists [Ref. 5.4: 05H90K].

Social isolation

Prevalence: In a prospective study of patients attending a pulmonary specialty clinic in the United States with a complaint of chronic cough, 80% (109/136) of patients reported that cough interfered with lifestyle and leisure; 79% (107/136) reported emotional issues, including frustration, irritation, or anger; and a third of patients aged <65 years reported that their spouse or roommate slept in another room because of their cough [Ref. 5.4: 0528XV].

In a separate prospective study conducted in the United States examining the effects of chronic cough on quality of life (n=28), chronic cough had a similar effect to that of severe,

disabling chronic obstructive pulmonary disease on multiple social domains, including ambulation, social interaction, sleep and rest, work, home management, and recreation [Ref. 5.4: 04YYWM].

Syncope

In a United Kingdom community survey of individuals who requested information about chronic cough in response to a radio broadcast, 10% (37/373) reported that they experienced cough syncope associated with the chronic cough [Ref. 5.4: 0527YB].

Co-prescribed medicinal products include: Fludrocortisone acetate, midodrine [Ref. 5.4: 05H90J].

Urinary stress incontinence

Prevalence: In retrospective study of 11,290 patients in the United States with specialist-diagnosed chronic cough 6% experienced stress incontinence [Ref. 5.4: 05G7NR]. In a recent study of 200 women with chronic cough (cough lasting > 8 weeks) who were consecutively recruited at a cough specialty center from March 2018 to August 2020, 64% (127/200) reported urinary stress incontinence exclusively associated with a cough episode. Of these 127 women, 119 (94%) reported that their urinary incontinence developed after the onset of their cough[Ref. 5.4: 05N08B]. In a longitudinal observational study of 80 adults with chronic cough attending a cough specialty clinic in the United States, a multivariable analysis demonstrated that lower cough-related quality of life was significantly associated with more severe urinary incontinence ($P<0.0001$) [Ref. 5.4: 0528XQ].

Co-prescribed medicinal products include: Alpha1-antagonists, H1-receptor antagonists, serotonin–noradrenaline reuptake inhibitors, anticholinergics, smooth muscle relaxants, tricyclic antidepressants, alpha-adrenergic agonists, and beta-3agonists.

Vomiting

Prevalence: In a retrospective study, of 11,290 patients in the United States with specialist-diagnosed chronic cough, vomiting was rarely experienced (0.9%) [Ref. 5.4: 05G7NR].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Gefapixant has been evaluated in a comprehensive non-clinical safety assessment program to support oral administration in humans. This assessment included safety pharmacology studies, in vitro and in vivo genetic toxicity studies and repeat-dose oral toxicity studies up to 3 months in duration in mice, up to 6 months in duration in rats and up to 9-months in dogs. Developmental and reproductive toxicity studies conducted with gefapixant included male and female fertility study in rats, embryo-fetal development studies in rats and rabbits, pre- and post-natal toxicity study in rats. Placental transfer was evaluated in rats and rabbits and lactational transfer was evaluated in study in rats. In addition, a six-month oral carcinogenicity study in rasH2 transgenic mice and a two-year oral carcinogenicity study in rats were conducted with gefapixant.

The important non-clinical safety findings are summarized in [Table SII.1]. In this document, the non-clinical/clinical exposure (AUC) and C_{max} ratios are calculated based on the clinical $AUC_{0\text{-}24hr}$ for gefapixant of 8280 ng*hr/mL (AUCss 0-12hr of 4140 ng*hr/mL multiplied by 2) and C_{max} of 531 ng/mL achieved at the recommended human dose of 45 mg BID.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Toxicity: Crystal-related uropathy: Urinary crystal formation and tissue injury to kidney, bladder and ureter were observed in rat and dog studies up to six months in rats and nine months in dogs. Majority of crystals and calculi collected from the tissues in rat and dog studies identified/composed of MK-7264. Urinary crystals in both rat and dog chronic toxicity studies were observed at lower doses (up to 225 mg/kg/day in rats and up to 50 mg/kg/day in dogs) with no histopathology findings. In the six-month repeat dose oral toxicity study in rats, crystals were observed in the urine at 75, 225 and 450 mg/kg/day. Microscopic changes in the kidney (distended tubules due to presence of crystalline material, degeneration of epithelial cells lining tubules and inflammation in the interstitium), ureter (dilatation and inflammation) and bladder (transitional cell hyperplasia) were observed at 450 mg/kg/day ($AUC_{0\text{-}24hr}$ = 70700 ng*hr/mL), and demonstrated reversibility following an 8-week treatment free period. No observed adverse effect level (NOAEL) for the 6-month rat study was at 225 mg/kg/day (4X and 7X the human $AUC_{0\text{-}24hr}$ and C_{max}, respectively, at 45 mg bid). In the nine-month repeat dose oral toxicity study in dogs, crystals were observed in the urine at 25, 50 and 100 mg/kg/day. Microscopic observation of focal, minimal tubular degeneration, involving occasional cortical tubules was observed in one male dog at 100 mg/kg/day ($AUC_{0\text{-}24hr}$ = 292000 ng*hr/mL) at the end of 9-month treatment	In a Phase 1 trial, healthy participants treated with gefapixant at 1800 mg BID for 14 days developed MK-7264 urinary crystals. In the Phase 3 trials (P027 and P030) where 15 mg and 45 mg were evaluated, specialized urine testing to identify gefapixant urinary crystals and medical monitoring to identify reports of urolithiasis were conducted. One participant in P030 in the 45 mg group was positive for MK-7264 crystalluria at Week 52. No renal findings were reported in that participant. Within the P027/P030 pooled data, urolithiasis (i.e., nephrolithiasis, calculus urinary, calculus bladder and ureterolithiasis) was reported in 8 of 686 participants in the 15 mg group, 4 of 683 participants in the 45 mg group, and 3 of 675 participants in the placebo group. The product label for gefapixant contains information in the adverse events section on urolithiasis.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
period. NOAEL for the 9-month dog study was at 50 mg/kg/day (24X and 26X the human $AUC_{0\text{-}24hr}$ and C_{max}, respectively, at 45 mg bid).	
Carcinogenicity: In a two-year carcinogenicity study in rats and 6-month carcinogenicity study in rasH2 transgenic mice, gefapixant showed no evidence of carcinogenic potential (no treatment related tumors) at exposures up to 9X (rats) and 4X (mice) the human exposures.	No evidence of carcinogenicity in non-clinical studies, therefore not a risk to humans.
Reproductive / Developmental Toxicity: Gefapixant had no effects on fertility, mating performance or early embryonic development in rats up to the highest dose tested, 675 mg/kg/day (approximately 9X the human AUC). Gefapixant showed no evidence of teratogenicity or embryo fetal lethality in rats and rabbits at exposures (AUC) that were 6X (rats) and 34X (rabbits) the exposure in humans. A slight reduction in rat fetal weights (6-7%), which was associated with maternal toxicity, was observed at an exposure approximately 11X the exposure in humans. In rabbits at a maternally toxic dose (due to decreases in food consumption, body weight loss and one abortion) of 1500 mg/kg/day (approximately 34X the human exposure), no adverse effects on embryo-fetal development were observed. Gefapixant had no effects on pre- and post-natal development in rats up to maternally toxic highest dose tested, 675 mg/kg/day (11X the exposure in humans). Studies in pregnant rats and rabbits showed that gefapixant is transferred to the fetus through the placenta, with fetal plasma concentrations of up to 21% (rats) and 25% (rabbits) that of maternal concentrations observed on gestation day 20. Gefapixant was excreted in milk of lactating rats when administered orally (up to 675 mg/kg/day) on lactation day 10, with milk concentrations 4 times that of maternal plasma concentrations observed 1-hour post dose on lactation day 10.	Animal data do not indicate harmful effects of gefapixant with respect to fertility, pregnancy and embryo-fetal development. There are no data from the use of gefapixant in pregnant women. Gefapixant is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether gefapixant is excreted in human milk. No human data on the effect of gefapixant on fertility are available.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

As of 17-Sep-2020, across the gefapixant clinical development program, 2,413 participants received at least 1 dose of gefapixant in the completed Phase 1 and Phase 2 and Phase 3 (P027 and P030) clinical studies. Exposure to gefapixant is summarized in Table SIII.1.

The Phase 1 program includes 18 completed studies (16 studies in healthy participants, 1 study that included both healthy participants and participants with renal impairment, and 1 additional study in participants with OSA). Across the completed studies, participants received gefapixant 10 mg to 1800 mg as single oral doses or 7.5 mg BID to 1800 mg BID for up to 14 days.

The Phase 2 program includes 13 completed studies. Of the completed studies, 10 studies assessed the effect of gefapixant on cough: chronic cough (5 studies), cough due to IPF (2 studies), cough due to viral-induced upper respiratory tract infection (1 study), and effect on cough reflex sensitivity (2 studies). Across the completed studies, participants received oral doses of gefapixant from 7.5 mg BID to 600 mg BID for up to 4 weeks and 7.5 mg BID to 50 mg BID for 12 weeks.

The Phase 3 program includes the 2 double-blind, randomized, placebo-controlled, global studies (P027 and P030) that are pooled for the primary safety evaluation. The two studies had identical entry criteria and dosing regimens. Each study had a Main Study period (12 weeks for P027 and 24 weeks for P030) followed by an Extension Study period (40 weeks for Study P027 and 28 weeks for P030), for a total treatment duration of 52 weeks. As of the 17-Sep-2020 database lock for this RMP, both studies are complete. The safety and tolerability assessment for the gefapixant chronic cough program relies predominantly on pooled data from Phase 3 studies. The exposure information for the pooled Phase 3 data is presented in Tables SIII.2 - SIII.5 below.

Table SIII.1: Participant Exposure to Gefapixant

	Phase 1	Phase 2	Phase 3	Total
MK-7264	448	596	1369	2413
Phase 1 trials include: P001, P002, P003, P007, P011, P017, P020, P022, P023, P024, P025, P026, P028, P032, P036, P039, P040, and P044. Phase 2 trials include: P004, P005, P006, P009, P010, P012, P013, P014, P015, P016, P019, P021 (an extension study of P010), and P033. Phase 3 trials include: P027 and P030.				

Source: [Table 5.3.5.3.3-cough: 3, 4, 5], [Ref. 5.3.4.2: P039MK7264: Figure 10-1]

Table SIII.2: Extent of Exposure to MK-7264 by Duration Safety Pool Across P027 and P030 All Participants as Treated

Duration of Exposure	Subjects	Subject Time (years)
Any exposure	1,369	1038.98
≥12 weeks	1,130	1017.64
≥24 weeks	1,033	985.88
≥52 weeks	633	630.68
Each subject is counted once on each applicable duration category row. Duration of exposure is calculated assuming one day of dosing = one day of exposure. The cutoff days for duration of exposure ≥12 weeks, ≥24 weeks, and ≥52 weeks are 84, 168, and 360, respectively.		

Source: [ISS: adam-adexsum]

Table SIII.3: Clinical Trial Exposure to MK-7264 by Dose Safety Pool Across P027 and P030 All Participants as Treated

Dose of Exposure	Subjects	Subject Time (years)
Any dose	1,369	1039.0
15 mg	686	558.6
45 mg	683	480.4
Each subject is counted once on each applicable dose category row. Duration of exposure is calculated assuming one day of dosing = one day of exposure.		

Source: [ISS: adam-adexsum]

Table SIII.4: Clinical Trial Exposure to MK-7264 by Age Category and Gender Safety Pool Across P027 and P030 All Participants as Treated

Age Category	Subjects			Subject Time (years)		
(years)	Male	Female	Total	Male	Female	Total
< 18	0	0	0	0.0	0.0	0.0
18 to 64	232	661	893	177.2	506.9	684.2
≥ 65	116	360	476	87.3	267.5	354.8
Total	348	1,021	1,369	264.5	774.5	1039.0
Duration of exposure is calculated assuming one day of dosing = one day of exposure.						

Source: [ISS: adam-adexsum]

Table SIII.5: Clinical Trial Exposure to MK-7264 by Race Safety Pool Across P027 and P030 All Participants as Treated

Race	Subjects	Subject Time (years)
American Indian Or Alaska Native	66	52.8
Asian	98	68.0
Black Or African American	30	20.9
Multiple	84	71.0
Native Hawaiian Or Other Pacific Islander	5	4.0
White	1,086	822.4
Total	1,369	1039.0
Duration of exposure is calculated assuming one day of dosing = one day of exposure.		

Source: [ISS: adam-adexsum]

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
		[Yes/No]	
Women who are pregnant or breast feeding	There were no data from any study on the use of MK-7264 in pregnant women, presence of MK-7264 in human milk, or the effects of MK-7264 on the breastfed infant, milk production, or human fertility. This criterion was applied in order to avoid potential harm to the unborn fetus or breastfeeding newborn.	Yes	N/A
Current smokers or patients who have ceased smoking within 12 months	Patients with chronic cough due to smoking should cease smoking as a first line treatment. Patients with chronic cough due to smoking do not meet the definition of RCC or UCC. The 12-month criterion was utilized because patients with chronic cough due to smoking show benefit from smoking cessation as early as 2 weeks but up to at least 6 months. This exclusion criterion was applied to ensure that the protocol was consistent with clinical practice/guidelines for the treatment of chronic cough	No	Cessation of smoking is consistent with clinical practice/guidelines for treatment of chronic cough. As such, this exclusion criterion will not be applicable in the post- marketing environment as the appropriate population is defined in the labeling.
History of anaphylaxis or cutaneous adverse drug reaction (with or without systemic symptoms) to sulfonamide antibiotics or other sulfonamide-containing drugs.	Gefapixant contains a sulfonamide moiety but is lacking an arylamine group (NH2) at the N4 position present in sulfonamide antimicrobials and is considered to be a non sulfonylarylamine. Despite information in the literature indicating that the risk of cross-reactivity between gefapixant and sulfonamide antibiotics is low, this exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	The prescribing information for gefapixant provides labeled warning regarding potential for hypersensitivity to sulfonamides.
Patients with (FEV1/FVC ratio <60%, chronic bronchitis, and former smokers with ≥20 pack year smoking history	Patients with significant lung disease do not meet the protocol definition of RCC or UCC or the intended treatment population. This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	This exclusion criterion will not be applicable in the post- marketing environment as the appropriate population is defined in the labeling.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
		[Yes/No]	
Patients on ACE inhibitors within the last 3 months	Most major clinical guidelines recommend that ACE-Inhibitors should be discontinued if they are identified as a cause of cough as should other drugs that are known to cause cough. Patients with a history of chronic cough suspected to be due to a drug do not meet the definition of RCC or UCC. This exclusion criterion was applied to ensure that the protocol was consistent with clinical practice/guidelines for the treatment of chronic cough.	No	Most major regional clinical guidelines for chronic cough recommend removing drugs known to cause cough. As such, this exclusion criterion will not be applicable in the post- marketing environment as the appropriate population is defined in the labeling.
Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 at Screening OR eGFR ≥30 mL/min/1.73 m2 and <50 mL/min/1.73 m2 at Screening with unstable renal function	Elimination of gefapixant is primarily through renal excretion. A Phase 1 study (P026), including 6 participants with severe renal impairment (eGFR <30 mL/min/1.73 m2) and 6 participants with end-stage renal disease (ESRD) (requiring hemodialysis) confirmed that participants with severe renal impairment would be expected to have higher drug exposure, to an extent that might be clinically meaningful. This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Modeling of the effect of renal impairment on gefapixant PK, incorporating data from across the development program, support the dosing recommendations for severe renal impairment that are provided in the prescribing information for gefapixant.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included as participants in the clinical development program There are no adequate and well-controlled studies of gefapixant in pregnant or nursing women. There is no information regarding the presence of gefapixant in human milk, or the effects of gefapixant on milk production or a breastfed infant. Across the program, pregnant or nursing women were excluded from study participation. Pregnancies or exposure to gefapixant during nursing that occurred during study participation were reportable safety events. There were two pregnancies reported during the 52 weeks of the Phase 3 studies. One participant in the gefapixant 45 mg group, discontinued study intervention (last dose taken on Day 310) due to pregnancy and completed the study off treatment on Day 366. The pregnancy outcome was a vaginal live birth delivery at 39 weeks gestation on Day 676. No congenital anomalies were reported at birth. Second participant, in the gefapixant 15 mg group, discontinued study intervention (last dose taken on Day 182) due to pregnancy and completed the study off treatment on Day 366. The pregnancy outcome was a vaginal live birth delivery at 37 weeks gestation on Day 412. The infant was reported as having no congenital anomaly or other abnormality.
Breastfeeding women	Not included in the pre-authorization clinical development program
Pediatric patients	Not included in the pre-authorization clinical development program
Participants with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2	There is limited information on participants with eGFR <30 mL/min/1.73 m2 in the clinical development program. One Phase 1 trial (P026) included 12 participants (6 with severe RI and 6 with ESRD requiring hemodialysis). These patients were not included in the Phase 3 program because they were not adequately studied prior to the initiation of Phase 3. If patients had a decrease in eGFR below 30 mL/min/1.73 m2 during the course of the Phase 3 program, they were evaluated by the investigator to determine if they were appropriate to continue in the study. There are no specific safety concerns related to participants with an eGFR <30 mL/min/1.73 m2. The prescribing information for gefapixant provides dosing recommendations for patients with severe renal impairment.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

As of 19-Jan-2023, gefapixant was approved in Japan (20-JAN-2022) and in Switzerland (24-MAY-2022) and is currently marketed in Japan.

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide distribution of gefapixant, for the cumulative period of 20-JAN-2022 [International Birth Date (IBD)] to 19-JAN-2023, is calculated from our Company's internal distribution data from the Financial Sharing Area database. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The estimated patient exposure was based upon the assumptions that every patient will take two 45 mg tablets/day, 365 days/year and have 100% compliance.

It is important to note that the estimated Patient Years of Treatment (PYT) are not equivalent to the absolute number of patients treated. It should also be noted that the overall PYT estimates are likely to underestimate the true number of patients exposed to gefapixant, due to the fact that PYT estimates are a calculated number of patients who could have been treated for one year based on the tablets distributed. However, since most patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher.

SV.1.2 Exposure

Cumulatively, for the period of 20-JAN-2022 through 19-JAN-2023, approximately 5,905,500 gefapixant 45 mg tablets were distributed. Cumulatively for this period, this accounts for approximately 8,090 Patient-Years of Treatment with gefapixant 45 mg tablets.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Gefapixant is available only through prescribing physicians and other health care providers with prescriptive authority. Neither gefapixant nor its components are known to possess addictive properties.

The Marketing Authorization Holder (MAH) has not been made aware of any reports of misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the prescribing information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised).

Hypersensitivity to sulfonamides

Hypersensitivity is a class-effect for sulfonamide antibiotics. Gefapixant contains a sulfonamide moiety but is lacking an arylamine group (NH_2) at the N4 position present in sulfonamide antimicrobials and is considered a non-sulfonylarylamine. Despite information that cross-reactivity between sulfonamide antibiotics and non-sulfonylarylamine, such as gefapixant, is considered unlikely, participants with a history of hypersensitivity to sulfonamides were excluded from the clinical program to avoid factors that may confound the evaluation of safety and efficacy of the clinical trials. In addition to the likelihood of a hypersensitivity reaction being low, the diagnosis and management of a hypersensitivity reaction are standard clinical practice; therefore, this risk does not warrant inclusion in the RMP. The warnings and precautions section of the label includes information stating that gefapixant should be used with caution in patients with known hypersensitivity to sulfonamides. No additional risk minimization measures or additional pharmacovigilance activities are warranted.

Urolithiasis

In preclinical studies, crystals and calculi collected from tissues in rat and dog studies were identified/composed of MK-7264. Renal calculi or urolithiasis were not observed in Phase 1 or 2 trials. Within Phase 3 (P027/P030 Pool), 8 events of urolithiasis (calculus urinary [n=2], and nephrolithiasis [n=6]) were reported in the 686 participants in the gefapixant 15 mg group with 4 events of urolithiasis (calculus bladder [n=1], calculus urinary [n=2], and nephrolithiasis [n=1]) reported in the 683 participants in the gefapixant 45 mg group compared to 3 events of urolithiasis (ureterolithiasis [n=1]) and nephrolithiasis [n=2]) in the 675 participants in the placebo treated group. Events of urolithiasis were not dose-related, and none of the participants with urolithiasis showed evidence of gefapixant urine crystals during protocol specified urine testing. These rates reflect a very low event rate of 1.4 per 100 patient years and 0.8 per 100 patient years in participants treated with 15 mg BID and 45 mg BID, respectively, compared to an event rate of 0.5 per 100 patient years in participants treated with placebo. Diagnosis, management, and prevention of urolithiasis is within standard clinical practice and does not require additional risk minimization measures or

additional pharmacovigilance activities. The specific preferred terms (PTs) for urolithiasis are included in the adverse reactions section of the label.

Table SVII.1.1.1 lists adverse drug reactions (ADRs) reported in patients receiving gefapixant 45 mg twice daily in Phase 3 clinical trials at 52 weeks as reflected in the summary of product characteristics (SmPC).

Table SVII.1.1.1: Adverse Reactions for Gefapixant 45 mg Twice Daily

System Organ Class	**Adverse Drug Reaction**
Infections and Infestations	
Common	Upper respiratory tract infection
Metabolism and nutrition disorders	
Common	Decreased appetite
Nervous system disorders	
Very Common	Dysgeusia*, Ageusia, Hypogeusia
Common	Taste disorder, Dizziness
Psychiatric disorders	
Common	Insomnia
Respiratory, thoracic and mediastinal disorders	
Common	Cough**, Oropharyngeal pain
Gastrointestinal disorders	
Common	Nausea, Diarrhoea, Dry mouth, Salivary hypersecretion, Abdominal pain upper, Dyspepsia, Hypoaesthesia oral, Paraesthesia oral
Renal and Urinary disorders	
Uncommon	Calculus urinary, Nephrolithiasis, Calculus bladder

* Dysgeusia was commonly reported as taste bitter, taste metallic or taste salty.

** Cough includes reports of 'worsening', 'exacerbation', 'increase', or 'increased' cough.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1.2.1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety concern	Benefit risk impact
Important identified risks	
None	N/A
Important potential risks	
Progression of respiratory tract infections and risk of development of pneumonia	Gefapixant 45 mg BID, indicated for use in adults with RCC or UCC, is a peripheral acting antitussive with a novel mechanism of action (MOA). The mechanism of action of gefapixant does not support suppression of the natural protective cough reflex. Review of safety data from participants in the P027/P030 Pool at 52 weeks, shows a low incidence (<0.1%) of symptoms suggestive of a loss of protective cough reflex and low (<1.6%) and comparable incidences of the individual preferred terms for pneumonia in the placebo and gefapixant 45 mg groups. As a first in class molecule, the Agency has requested that 'Progression of respiratory tract infections and risk of development of pneumonia' be included as an important potential risk.
Missing information	
Use in patients with comorbid obstructive sleep apnoea	The inclusion of this missing information, to be followed post-approval with routine pharmacovigilance, may help to characterize the safety profile of gefapixant 45 mg BID in patients with RCC and UCC and comorbid OSA.
Use in pregnancy and lactation	The inclusion of this missing information will characterize the safety profile of gefapixant in these populations and will further assist health care providers who are prescribing gefapixant to women for the treatment of RCC or UCC who are pregnant, may become pregnant or who are breastfeeding.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Progression of respiratory tract infections and risk of development of pneumonia
Missing information	Use in patients with comorbid obstructive sleep apnoea Use in pregnancy and lactation

SVIII.1 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVIII.2 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVIII.2.1 Presentation of Important Identified Risks and Important Potential Risk

Important Potential Risk - Progression of respiratory tract infections and risk of development of pneumonia

Potential Mechanisms:

The MOA and the safety profile of gefapixant are well described in the SmPC. There is no known mechanistic basis for the potential risk of progression of respiratory tract infections and the risk of development of pneumonia. Gefapixant is a peripheral acting antitussive with a novel MOA that preserves the protective cough reflex. P2X3 receptors are ATP-gated ion channels found on sensory C-fibers of the vagus nerve in the airways. While P2X3 mRNA is expressed by both jugular and nodose A-delta and C-fibers, the activation of these fibers differs. It is the A-delta fibers that are responsive to mechanical stimuli and thus serve as the primary mediators of protective cough. The A-delta fibers may provide a defensive mechanism for the airways from aspiration and can be activated to induce cough even in unconscious animals [Ref. 5.4: 07WQB3]. In contrast, the C-fibers respond to chemical stimuli, including ATP, and are involved in mediating inflammatory cough and chemically induced cough. In the Phase 3 safety data at 52 weeks, the overall incidences of AEs associated with pneumonia and lower respiratory tract infections (LRTIs) were low (≤4.5%). The incidences of the individual preferred terms for pneumonia and LRTI were also low (≤1.6%) and comparable in the placebo and gefapixant 45 mg groups.

Evidence Source and Strength of Evidence:

Gefapixant is a first in class molecule for the treatment of RCC and UCC in adults. The indications for use, warnings and precautions, and the safety profile of gefapixant are well

described in the SmPC. The Agency has requested that progression of respiratory tract infections and risk of development of pneumonia, be included as an important potential risk in the RMP. It is the opinion of the Agency that, as a first in class molecule, the mechanism of action for gefapixant is not fully explained and that further characterized of this important potential risk is needed.

Characterization of the Risk:

The overall incidences of AEs associated with pneumonia and LRTIs were low (≤4.5%) in the placebo and gefapixant 45 mg groups. The incidences of individual pneumonia PTs (atypical pneumonia, pneumonia, pneumonia bacterial, pneumonia staphylococcal, and pneumonia streptococcal) were low (≤1.6%) and comparable between the 2 groups (see Table). One participant in the gefapixant 45 mg group reported a serious AE of pneumonia (caused by *Haemophilus influenzae*); none were reported in the placebo group.

Table SVIII.2.1.1: Participants With Pneumonia and Lower Respiratory Tract Infections Adverse Events (Incidence > 0% in One or More Treatment Groups) Safety Pool Across P027 and P030 over the Period of 52 Weeks All Subjects as Treated

	Placebo		Gefapixant 45 mg BID	
	n	(%)	n	(%)
Participants in population	676		683	
with ≥ pneumonia and lower respiratory tract infections	20	(3.0)	28	(4.1)
with no pneumonia and lower respiratory tract infections	656	(97.0)	655	(95.9)
Infections and infestations*	**20**	**(3.0)**	**28**	**(4.1)**
Atypical pneumonia	0	(0.0)	0	(0.0)
Lower respiratory tract infection	9	(1.3)	11	(1.6)
Pneumonia	5	(0.7)	10	(1.5)
Pneumonia bacterial	0	(0.0)	0	(0.0)
Pneumonia staphylococcal	0	(0.0)	0	(0.0)
Pneumonia streptococcal	1	(0.1)	0	(0.0)
Respiratory tract infection	5	(0.7)	7	(1.0)

Every subject is counted a single time for each applicable row and column.
* Preferred terms for Lower respiratory tract infection viral and Respiratory tract infection viral were excluded.
This report is generated based on the database locks of P027 and P030 (both taken on 04MAR2020).

Risk Factors and Risk Groups:

Individuals with chronic cough experience a higher incidence of pneumonia, as well as, higher incidences of upper and lower respiratory infections, than individuals without chronic cough. These findings are from a retrospective observational cohort study conducted using administrative data from the Kaiser Permanente Southern California (KPSC) Research Data Warehouse among patients diagnosed with chronic cough and those without a diagnosis of chronic cough [Ref. 5.4: 05G7NR].

Preventability:

The SmPC for gefapixant under Section 4.1, Therapeutic indications, Section 4.2, Posology and method of administration, and Section 4.8, Undesirable effects provides information for healthcare professionals to inform on the safe use of gefapixant. Section 4.4, Special warnings and precautions for use, recommends that patients who develop an acute lower respiratory tract infection during treatment with gefapixant should consult a healthcare professional regarding care.

Impact on the Risk-Benefit Balance of the Product:

This important potential risk will be monitored through routine pharmacovigilance activities and reported in the PSUR. Information that further characterizes the risk will be included in the PSUR and reported appropriately per regulatory requirements.

Public Health Impact:

No public health impact related to progression of respiratory tract infections and risk of development of pneumonia would be anticipated.

SVIII.2.2 Presentation of the Missing Information

Use in patients with comorbid obstructive sleep apnoea

Evidence Source:

The safety profile of gefapixant 45 mg BID in patients with RCC or UCC and untreated comorbid obstructive sleep apnoea (OSA) is not known but is not expected to differ from the safety profile of gefapixant 45 mg BID in patients who either do not have OSA or who have adequately treated OSA.

In a study (P039) of 19 participants with moderate to severe OSA who were not using positive airway pressure (PAP), gefapixant 180 mg QHS compared to placebo was associated with a lower mean oxygen saturation (SaO2) and a higher proportion of time with SaO2 <90% across all sleep stages but no difference in the Apnea/Hypopnea Index (AHI), which was the primary endpoint. The effect of gefapixant at doses other than 180 QHS on SaO2 has not been evaluated in any patient population.

The SaO2 findings in P039 are not expected to be a safety concern for patients with RCC or UCC. P039 tested a dose of gefapixant expected to achieve a higher exposure than is recommended for RCC and UCC, and the enrollment criteria for participants in P039, such as high AHI and lack of PAP treatment, made them particularly likely to have oxygen desaturation. OSA therapies (such as PAP) that mitigate apneic and hypopneic episodes also mitigate hypoxemia.

The AEs observed in P039 were generally similar to those in the P027/P030 Pool. No clinically meaningful trends were noted in the safety laboratories, vital signs, or ECGs with treatment with gefapixant.

In the P027/P030 Pool, approximately 6% of participants reported a medical history of sleep apnoea syndrome or apnoea. In this subset of participants, the overall incidences of AEs by intervention group were generally comparable to the incidences in the P027/P030 Pool.

Treatment of patients with OSA is considered standard clinical practice including the use of PAP to treat patients with moderate to severe OSA. Additionally, some evidence suggests that OSA patients with chronic cough experience improvement in their chronic cough when treated with PAP [Ref. 5.4: 05MV3Z, 05JCB0].

The Special warnings and precautions section of the SmPC includes information stating that for patients with OSA, appropriate treatment for OSA should be considered prior to initiating treatment with gefapixant 45 mg BID.

Population in Need of Further Characterisation:

The effect of gefapixant 45 mg BID in patients with RCC or UCC and comorbid OSA is not known. Study P039 was conducted in participants with OSA, not in participants with RCC or UCC and at a dose of gefapixant (180 mg QHS) expected to achieve a higher exposure than is recommended for RCC and UCC.

Use in pregnancy and lactation

Evidence Source:

There are no adequate studies of gefapixant use during pregnancy or lactation. Across the program, pregnant or nursing women were excluded from study participation.

No adequate human data are available to establish whether or not gefapixant poses a risk to pregnancy outcomes. Gefapixant use in women during pregnancy has not been evaluated. In animal reproduction studies, oral administration of gefapixant to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity or embryofetal lethality at exposures (area under the curve [AUC]) that were 6 times (rats) and 34 times (rabbits) the exposure in humans at the recommended human dose (RHD). A slight reduction in rat fetal weights, which was associated with maternal toxicity, was observed at an exposure approximately 11 times the exposure in humans at the RHD. Prescribing information includes, as a precautionary measure, it is preferable to avoid the use of gefapixant during pregnancy and in women of childbearing potential not using contraception.

It is unknown whether gefapixant is present in human milk, affects human milk production, or has effects on the breastfed infant. Gefapixant is present in the milk of lactating rats. In a lactation study, gefapixant was excreted in milk of lactating rats when administered orally (up to 675 mg/kg/day) on lactation day 10, with milk concentrations 4 times that of maternal plasma concentrations observed 1-hour post dose on lactation day 10. Prescribing information advises decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with gefapixant while taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

We do not anticipate a risk to pregnant women. Pregnancies or exposure to gefapixant during nursing that occurred during study participation were reportable safety events.
In the P027/P030 Pool, 2 participants (1 in the gefapixant 45 mg group and 1 in the gefapixant 15 mg group) discontinued study intervention due to pregnancies. Both full-term pregnancies resulted in live births. No congenital or other abnormalities were reported. There were no adverse event reports of maternal exposure during breast feeding during P027 and P030.

Based on a specific request of the European Medicines Agency (EMA), Use in pregnancy and lactation was added to the risk profile of gefapixant, classified as Missing Information.

Population in Need of Further Characterisation:

There are insufficient data from the use of gefapixant in pregnant women to determine the safety of gefapixant in infants exposed during pregnancy or while breastfeeding. Studies in animals have shown no evidence of teratogenicity or embryofetal lethality. Gefapixant was detected in breast milk in studies performed in rats. No studies have been performed to determine if gefapixant is released into breast milk of nursing mothers treated with gefapixant.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not applicable

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance studies that are required for gefapixant.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for gefapixant.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important potential risk: Progression of respiratory tract infections and risk of development of pneumonia	Routine Risk Communication: SmPC sections: 4.1 Therapeutic indication, 4.2 Posology and methods of administration, 4.4 Special warnings and precautions, and 4.8 Undesirable effects PL sections: 1 What gefapixant is and what it is used for, 2 What you need to know before you take gefapixant, Warnings and precautions, 3 How to take gefapixant, How much to take, and 4 Possible side effects Other routine risk minimisation measures beyond the Product Information: None Legal status: Prescription only medicine
Missing information: Use in patients with comorbid obstructive sleep apnoea	Routine Risk Communication: SmPC section 4.4 Special warnings and precautions PL section 2 What you need to know before you take gefapixant, Warnings and precautions Other routine risk minimisation measures beyond the Product Information: None Legal status: Prescription only medicine
Missing information: Use in pregnancy and lactation	Routine Risk Communication: SmPC section 4.6 Fertility, Pregnancy and Lactation PL section 2 What you need to know before you take gefapixant, Pregnancy and breast-feeding Other routine risk minimisation measures beyond the Product Information: None Legal status: Prescription only medicine

V.2 Additional Risk Minimization Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important potential risk: Progression of respiratory tract infections and risk of development of pneumonia	Routine risk minimization measures: SmPC sections: 4.1 Therapeutic indication, 4.2 Posology and methods of administration, 4.4 Special warnings and precautions and 4.8 Undesirable effects PL sections: 1 What gefapixant is and what it is used for, 2 What you need to know before you take gefapixant, Warnings and precautions, 3 How to take gefapixant, How much to take, and 4 Possible side effects Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: Use in patients with comorbid obstructive sleep apnoea	Routine risk minimization measures: SmPC section 4.4 Special warnings and precautions PL section 2 What you need to know before you take gefapixant, Warnings and precautions Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: Use in pregnancy and lactation	Routine risk minimization measures: SmPC section 4.6 Fertility, Pregnancy and Lactation PL section 2 What you need to know before you take gefapixant, Pregnancy and breast-feeding Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for gefapixant tablets

This is a summary of the RMP for Lyfnua. The RMP details important risks of Lyfnua, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information) of Lyfnua.

The SmPC for Lyfnua and its package leaflet give essential information to healthcare professionals and patients on how Lyfnua should be used.

This summary of the RMP for Lyfnua should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of RMP for Lyfnua.

I. The Medicine and What it is Used For

Lyfnua is authorised for treatment of refractory or unexplained chronic cough (see SmPC for the full indication). It contains gefapixant as the active substance and it is given by oral administration.

Further information about the evaluation of benefits of Lyfnua can be found in the EPAR for Lyfnua, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Lyfnua, together with measures to minimise such risks and the proposed studies for learning more about the risk of Lyfnua, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Lyfnua are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lyfnua. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Progression of respiratory tract infections and risk of development of pneumonia
Missing information	Use in patients with comorbid obstructive sleep apnoea Use in pregnancy and lactation

II.B Summary of Important Risks

Table II.B.1: Progression of Respiratory Tract Infections and Risk of Development of Pneumonia

Evidence for linking the risk to the medicine	Gefapixant is a first in class molecule for the treatment of RCC and UCC in adults. The indications for use, warnings and precautions, and the safety profile of Lyfnua are well described in the SmPC. While there is no mechanistic or clinical evidence indicating a risk of progression of respiratory tract infections and risk of development of pneumonia, this risk is included as potentially important recognizing that gefapixant is a first in class molecule and that further characterization of this important potential risk would be helpful.
Risk factors and risk groups	Individuals with chronic cough experience a higher incidence of pneumonia, as well as, upper and lower respiratory infections, than individuals without chronic cough.
Risk minimisation measures	Routine risk minimisation measures SmPC sections: 4.1 Therapeutic indication, 4.2 Posology and methods of administration, 4.4 Special warnings and precautions and 4.8 Undesirable effects PL sections: 1 What Lyfnua is and what it is used for, 2 What you need to know before you take Lyfnua, Warnings and precautions, 3 How to take Lyfnua, How much to take, and 4 Possible side effects Additional risk minimisation measures: None.

Table II.B.2: Use in Patients with Obstructive Sleep Apnoea

Risk minimisation measures	Routine risk minimsation measures SmPC section 4.4 Special warnings and precautions PL section 2 What you need to know before you take Lyfnua, Warnings and precautions Additional risk minimisation measures: None.

Table II.B.3: Use in Pregnancy and Lactation

Risk minimisation measures	Routine risk minimisation measures SmPC section 4.6 Fertility, Pregnancy and Lactation PL section 2 What you need to know before you take Lyfnua, Pregnancy and breast-feeding Additional risk minimisation measures: None.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lyfnua.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Lyfnua.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable