Date: 12 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lyfnua

International non-proprietary name: gefapixant
Pharmaceutical form: film-coated tablets
Dosage strength(s): 45 mg
Route(s) of administration: oral
Marketing Authorisation Holder: MSD Merck Sharp & Dohme AG
Marketing Authorisation No.: 68065
Decision and Decision date: approved on 24 May 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance *gefapixant* of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Lyfnua is indicated for the treatment of refractory chronic cough (RCC) and unexplained chronic cough (UCC) in adult patients.

2.2.2 Approved Indication

Lyfnua is indicated in adults for the treatment of refractory chronic cough or unexplained chronic chough.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The recommended dose of gefapixant is 45 mg twice daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	11 March 2021
Formal control completed	15 March 2021
List of Questions (LoQ)	21 June 2021
Answers to LoQ	16 September 2021
Predecision	14 December 2021
Answers to Predecision	11 February 2022
Labelling corrections	12 April 2022
Answers to Labelling corrections	10 May 2022
Final Decision	24 May 2022
Decision	approval

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3 Medical Context

A cough is characterised by rapid expulsions of air from the lungs which are triggered by irritation of the respiratory tract or voluntarily. Involuntary cough is a polysynaptic reflex. It is mediated via sensory nerve fibres of the vagus nerve by receptors located primarily on the mucosa of the respiratory tract from the pharynx to the bronchioles.

Cough receptors can be subdivided into the following groups:

- mechano-sensitive, acid-sensitive, myelinated Aδ fibres
    - rapidly adapting mechanoreceptors (RAR)
    - slowly adapting mechanoreceptors (SAR)
- unmyelinated C fibres which differ from Aδ fibres in that they are not sensitive to mechanical stimuli. However, they can be activated by pro-inflammatory mediators (e.g. following inhalation of allergens or chemical irritants), osmotic and cold stimuli.

Clinical manifestations and causes

Chronic cough is defined in specialist circles as a cough that persists for longer than eight weeks. It is the common, and sometimes the only, symptom of a broad spectrum of disorders with different prognoses and different therapeutic approaches.

Unexplained chronic cough (UCC) and chronic refractory cough (CRC)

In relevant studies, between 0% and 46% of patients with chronic cough were unclear about its cause. Yet even if a likely cause can be identified, the cough may persist despite targeted therapy and an improvement in the underlying disorder. This is then referred to as unexplained chronic cough (UCC) or chronic refractory cough (CRC).

This is how chronic refractory cough (CRC) and unexplained chronic cough (UCC) were defined during the clinical development of gefapixant.

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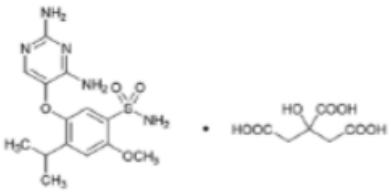
4 Quality Aspects

4.1 Drug Substance

Gefapixant citrate is a new drug substance within the meaning of ICH Q6A; it is not monographed in the Ph. Eur. or any other pharmacopoeia.

INN:	Gefapixant
Chemical name:	2,4-Diamino-5-[4-methoxy-2-(propan-2-yl)-5-sulfamoylphenoxy]pyrimidin-1-ium 3-carboxy-2- (carboxymethyl)-2-hydroxypropanoate (citrate salt)
Molecular formula (citrate salt):	C14H19N5O4S x C6H8O7
Molecular mass (citrate salt):	545.52 g/mol
Molecular mass (free base):	353.40 g/mol



Molecular structure:

Physico-chemical properties:
Gefapixant citrate is a white to light yellow powder. Gefapixant has no chiral centre and therefore exhibits no stereoisomerism. The manufacturing process reliably delivers the commercial crystalline anhydrate (Form 1).

Synthesis:
The synthesis of the drug substance has been adequately described and the process is controlled with appropriate in-process controls and tests for isolated intermediates. The quality of the starting materials, reagents, solvents and auxiliary materials used in the manufacturing process of gefapixant citrate is adequately controlled.
The development of the commercial manufacturing process for gefapixant citrate drug substance followed a systematic risk-based approach which has been addressed in suitable detail. A clear overview of batches used in development, toxicological, preclinical and clinical studies, validation and stability has been presented. Full batch analytical data are provided. Changes introduced have been presented in sufficient detail and have been justified. Based on the outcome of development studies, proven acceptable ranges (PARs), critical process parameters (CPPs), in-process controls (IPCs) and specifications for raw materials, intermediates and drug substance have been defined.

Structure elucidation:
The structure of gefapixant citrate has been fully elucidated using several analytical techniques including FT-IR, 1H- NMR & 13C- NMR, MS, UV and single crystal X-ray crystallography. The polymorphic form has been proven by X-ray powder diffraction. Potential impurities have been adequately discussed and, based on a detailed evaluation, the presence of nitrosamines in the gefapixant citrate drug substance can be excluded.

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Specification:
The active substance specification is set according to ICH Q6A and includes tests for appearance, identity by IR, water content, citrate content, residual solvents (GC), impurities (HPLC), assay (HPLC) and particle size distribution (laser light diffraction).
Limits for impurities are set according to ICH Q3A and are considered appropriate.
The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines.
Batch analysis data are provided for a number of batches. The analytical results are in full compliance with the specified limits and show only little variability with respect to the individual parameters tested, thus demonstrating a reliable and reproducible manufacturing process with consistent results from batch to batch.

Container-closure system:
The container-closure system for the final API (LDPE bags in a fibre drum container) is adequately described and its suitability is assured.

Stability:
Appropriate stability data have been generated, resulting in a suitable retest period when packaged in the packaging type as described above. Furthermore, photostability has been tested in compliance with Q1B during validation studies and demonstrates that the drug substance is not affected by light.

4.2 Drug Product

Description and composition:
The finished drug product is supplied as an immediate-release, film-coated tablet for oral use, containing 45 mg gefapixant free base delivered as a citrate salt. The final drug product is adequately described. The description is in compliance with information presented in Module 1 and the SPC.

Pharmaceutical development:
The excipients chosen are typical for this type of dosage form and are used in common quantities. Formulation and manufacturing development have been adequately described. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the film coating which is specified in a suitable in-house specification. No novel excipients are used in the finished product formulation.

The dissolution method used in development and QC of the drug product is described systematically and acceptably overall and the discriminatory power is demonstrated. Based on the dissolution profile of the clinical reference batch, the proposed dissolution specification for release can be accepted. The specification is in line with the EMA's reflection paper on dissolution specification, MA/CHMP/CVMP/QWP/336031/2017.

Development of the manufacturing process for the final tablet is pursued systematically in a scientific approach. Within this approach, critical process parameters have been adequately considered and results from DoE studies have been adequately discussed and demonstrate that the manufacturing process is well understood. Based on the outcome of these studies, critical process parameters have been identified and critical control points have been defined. Target points have been set and used to define suitable IPCs.

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Manufacture:
The drug product is manufactured by a standard manufacturing process which includes dry blending, compression and coating. Process parameters and in-process controls are defined in acceptable detail. During development it was demonstrated with a number of batches that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Furthermore, it is certified that formal validation studies within an acceptable process validation scheme will be performed on full commercial scale batches post approval. An acceptable process validation scheme including a suitable testing and sampling plan is presented.

Specification:
Adequate tests and acceptance criteria for release and at shelf-life are established for the control of the finished product. The tested parameters at release (including IPC) and shelf-life are in compliance with the Ph. Eur. monograph “tablets” and ICH-Guideline CPMP/ICH/367/96 and include the parameters description, identification tests, assay (HPLC), degradation products (HPLC), dissolution and uniformity of dosage units (Ph. Eur.). All the analytical procedures are adequately described and non-compendial methods are validated according to the current requirements of ICH Q2(R1). Batch analysis data have been provided. The results are within the specifications and consistent from batch to batch.
Degradation products are adequately characterised and a suitable discussion on elemental impurities and the risk of N-nitrosamines is provided.

Container-closure system:
The presented primary packaging system, white PVdC/PE/PVC blister with aluminium lidding foil, is standard for solid formulations. The proposed container-closure system is acceptably described and its suitability is demonstrated.

Stability:
Appropriate stability data have been generated in the packaging material for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was established. The storage recommendation is “Do not store above 25°C”.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product is demonstrated.

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5 Nonclinical Aspects

The nonclinical development programme for Lyfnua with the new active substance gefapixant followed relevant ICH guidelines. The pivotal studies for safety assessment were performed in compliance with GLP regulations.

5.1 Pharmacology

In vitro, gefapixant was shown to be a selective P2X3 receptor antagonist (IC_{50} approximately 30 to 70 nM) but had no activity on other P2X channels studied.

In vivo, gefapixant has not been evaluated in nonclinical models of cough or airway hyperexcitability. Although efficacy of gefapixant was not demonstrated for the requested indication, its ability to interact with the P2X3 receptor was shown in a number of rat models with other endpoints. In these models, gefapixant displayed anti-nocifensive effects, which were not related to a concomitant effect on locomotor activity.

In a secondary pharmacodynamic screening assay using a panel of 73 different receptors, ion channels or enzyme targets as well as 121 kinases, the applicant did not identify any off-target activity at a clinically relevant concentration.

Gefapixant was evaluated in a core battery of *in vitro* and *in vivo* studies to assess effects on cardiovascular, respiratory and central nervous system (CNS) function according to ICH S7A/B, as well as for effects on the renal/urinary system and gastrointestinal tract. Gefapixant had no effects on respective parameters.

5.2 Pharmacokinetics

The pharmacokinetics of gefapixant were studied in rats and dogs. Oral bioavailability was ≥ 38% in rats and ≥ 81% in dogs. Systemic plasma clearance ranged from 2.4 mL/min/kg in dogs to 29.5 mL/min/kg in rats. Elimination half-lives were about 4 hours in both species and comparable to humans (6-10 hours).

Following repeated daily dosing in rats and dogs, systemic exposure to gefapixant generally increased in a less than dose-proportional manner. The investigations identified neither any sex-related differences nor an obvious trend of accumulation in any of the nonclinical species.

In vitro plasma protein binding of gefapixant in rats, dogs and humans was similar (unbound fractions 48%, 41% and 45% respectively). ^{14}C-gefapixant-related radioactivity distributed widely throughout tissues, crossed the placenta and was excreted into milk. No measurable radioactivity was detected in the lens of the eye or in tissues of the CNS, indicating that gefapixant did not cross the blood-brain barrier. It transiently bound to melanin-containing tissues in the pigmented rat.

The applicant investigated the *in vitro* metabolic profile of gefapixant in liver microsomes and hepatocytes of mice, rats, rabbits, dogs and humans. Metabolism in liver microsomes and hepatocytes was limited in all species and gefapixant was also metabolically stable *in vivo*. Unchanged gefapixant was the major component observed in plasma samples after oral dosing in rats, dogs and humans. No unique metabolites were identified in human hepatocytes.

In nonclinical species and humans, gefapixant was mainly eliminated unchanged via urinary excretion, with metabolism as a minor elimination pathway.

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5.3 Toxicology

The toxicological profile of gefapixant was evaluated in mice, rats, rabbits (reproductive toxicity) and dogs. The selection of rat and dog for toxicological assessment is appropriate, as P2X receptors are present in mammalian cells and the applicant confirmed experimentally that the rat is a pharmacologically relevant species. Furthermore, the metabolism of gefapixant in both species is comparable to that in humans. The route of administration and frequency of dosing in the nonclinical studies are consistent with the proposed clinical setting.

Pivotal repeat-dose oral toxicity studies were conducted up to 26 weeks in rats (doses: 0, 75, 225 or 450 mg/kg/day) and 39 weeks in dogs (doses: 25, 50 or 100 mg/kg/day). A 4-week toxicity study was conducted in rasH2 wild-type mice (doses: 150, 500 or 1500 mg/kg/day) for dose selection for the 6-month carcinogenicity study in rasH2 transgenic mice.

Repeated doses of up to 150 mg/kg three times daily (TID) in rats (450 mg/kg/day) and 50 mg/kg twice daily (BID) in dogs (100 mg/kg/day) were tolerated well overall in both species.

The main target organ of gefapixant in the nonclinical species was the urogenital system due to the deposition of precipitated gefapixant crystals. Urine crystals in rats were observed at ≥ 75 mg/kg/day, but changes in urine parameters, histopathology findings and inflammatory response were only observed at the high dose of 450 mg/kg/day. Histological changes occurred in the kidney (distended tubules due to the presence of crystalline material, degeneration of epithelial cells lining tubules and inflammation in the interstitium), ureter (dilatation and inflammation) and urinary bladder (transitional cell hyperplasia). Urine crystals also occurred in dogs at all dose levels with microscopic findings limited to the kidney (minimal focal tubular degeneration of cortical tubules). Gefapixant-related microscopic findings showed a tendency towards reversibility in rats or were reversible in dogs following an 8-week treatment-free period.

The NOAELs for rats and dogs were 225 mg/kg/day and 50 mg/kg/day and the corresponding safety margins are low in rats (4-fold) and substantial in dogs (24-fold). The findings related to drug crystallisation in the urinary tract are not considered to be a significant human risk since no signs or symptoms of injury to the urinary tract were observed in healthy participants who received a high dose of 1800 mg gefapixant BID for up to 14 days.

Gefapixant was negative in *in vitro* and *in vivo* genotoxic assays according to ICH S2 (R1).

Gefapixant was not carcinogenic in rats and in transgenic mice at doses up to 300 mg/kg/day and 500 mg/kg/day, which is 9-fold and 4-fold the systemic exposure in humans at the recommended dose of 45 mg BID.

Gefapixant did not affect the fertility of male and female rats at doses up to 675 mg/kg/day, which corresponds to an exposure of approximately 9-fold the clinical exposure. In embryo-fetal development studies, maternal toxicity was observed in rats at 675 mg/kg/day and rabbits at 1500 mg/kg/day. Decreased fetal body weights occurred in rats at maternally toxic doses. At the NOAELs for maternal and development toxicity, the exposures based on AUC in rats and rabbits are 6- and 34-fold the clinical exposure at 90 mg/day. In the pre- and postnatal developmental toxicity study in rats, gefapixant induced maternal toxicity in F0 females at 675 mg/kg/day (exposure 11-fold the clinical exposure). No gefapixant-related effects were noted in the F1 generation up to this dose level. The recommendations for use during pregnancy and for breastfeeding in the Information for healthcare professionals are adequate.

Gefapixant was not phototoxic in the *in vitro* 3T3 Neutral Red uptake test.

Impurities are controlled according to ICH Q3A/B and ICH M7. There are no concerns about the excipients.

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Based on the ERA, the risk for the environment is low.

The nonclinical safety specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use.

Juvenile animal studies were not conducted. Gefapixant is not intended for use in a paediatric population.

5.4 Nonclinical Conclusions

In conclusion, a comprehensive study package covering pharmacology, pharmacokinetics and toxicology has been submitted to characterise the pharmaco-toxicological profile of gefapixant. All nonclinical data relevant to safety are mentioned in the Information for healthcare professionals. From a nonclinical perspective, approval may be granted in the proposed indication.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Data base: Seventeen completed clinical pharmacology studies were submitted, in which a total of 408 healthy subjects and 18 patients with renal impairment received at least one dose of gefapixant.

Ten studies investigated the PK of gefapixant after single and multiple doses alone or in combination with pyrimethamine or pitavastatin in healthy fasted or fed volunteers, healthy elderly and younger subjects, in Japanese subjects or in patients with renal impairment.

Seven further studies were part of the biopharmaceutics programme.

Across the Phase 1 studies, subjects received gefapixant doses ranging from 10 mg to 1800 mg as single oral doses or 7.5 mg BID to 1800 mg BID for up to 14 days.

Bioanalytical methods: All bioanalytical methods for the determination of gefapixant in plasma and urine were adequately validated in line with current regulatory requirements. A method for the routine determination of gefapixant metabolites was not required as gefapixant is the predominant moiety in plasma.

Biopharmaceutical development: Several tablet formulations were employed during the course of clinical development. The tablet formulation intended for commercialisation was shown to be bioequivalent to the tablet formulation used in the Phase 3 studies. Bridging to prior tablet formulations was accomplished in earlier stages of clinical development.

6.1.1 ADME

Absorption
Gefapixant is rapidly absorbed following oral administration with median T_{max} values of 1 to 4 h. The absolute bioavailability was not determined in view of the poor solubility of gefapixant. The mass balance study demonstrated a 78% urinary recovery of gefapixant and metabolites, which indicates near complete absorption of gefapixant. Co-administration of food and proton pump inhibitors did not have a clinically relevant impact on gefapixant exposure.

Pharmacokinetics after multiple doses
Following the proposed dose, steady-state is reached within 2 to 3 days with modest accumulation (1.4 to 1.5-fold).

Distribution
Based on popPK analysis, the mean value for V/F is 137.8 L (sum of Vc and Vp: 105 L and 32.8 L). The plasma protein binding is low (55%), independently of gefapixant concentration and species, with predominant binding to albumin. The blood-to-plasma concentration ratio in human whole blood is 1.1. Gefapixant exhibits low passive permeability.

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Metabolism and excretion
Gefapixant is metabolically stable. Metabolism (via CYPs or UGTs) is a minor pathway of gefapixant elimination, with approximately 12% and 2% of the dose recovered as metabolites in urine and faeces respectively. In plasma, the parent compound gefapixant accounted for approximately 87% of the total radioactivity. Several minor metabolites were identified in trace amounts. No metabolite was identified that was unique to humans. In addition, in vitro incubation of gefapixant with recombinant human cytochrome-450 (CYP) isoforms (CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4) indicated the metabolic stability of gefapixant. Gefapixant is primarily excreted via urine (overall: 76% of the administered dose; 64% as unchanged parent, 12% as metabolites); faecal excretion is a minor pathway with an overall recovery of 22 % of the administered dose (20% as unchanged parent, 2% as metabolites). Based on the popPK analysis the geometric mean CL/F is 10.8 L/h with a terminal elimination half-life ranging from 6 to 10 h.

Dose proportionality
In the dose range of 10 mg to 450 mg gefapixant, exposure (Cmax and AUC) increases in a dose-proportional manner. At higher doses less than proportional increases were observed.

6.1.2 Special Populations / Intrinsic Factors

Individual studies and the popPK analysis indicated the absence of a clinically meaningful effect of demographics on exposure to gefapixant.

In view of the low metabolic clearance, no dedicated hepatic impairment study was performed.

Based on the results of a renal impairment study and a popPK analysis no gefapixant dose adjustments are required in patients with mild and moderate renal impairment, while a dose reduction to 45 mg QD is recommended in patients with severe renal impairment.

Healthy volunteers vs. patients: There are no differences in exposure in patients vs. healthy volunteers.

6.1.3 Interactions

CYP enzymes: Gefapixant does not inhibit the CYP forms 1A2, 2B6, 2C8, 2C9, 2C19, 2E1 or CYP3A4/5 and does not inhibit 2D6 at clinically relevant concentrations. There was also no time-dependent gefapixant-mediated inhibition of these enzymes. Gefapixant does not induce the CYP forms CYP1A2, 2B6, 2C9 or 3A4. Thus, no dedicated *in vivo* interaction study was performed to investigate the potential of a CYP-mediated interaction with gefapixant as a victim or as a perpetrator, which is acceptable.

Transporters: Gefapixant is not a substrate of the transporters OAT1, OAT3 or OCT2). Gefapixant was, however, identified as a substrate of the transporters P-gp, BCRP and MATE1 and MATE2K. The *in vivo* potential for an interaction with gefapixant as a substrate of P-gp and BCRP can be considered low. An *in vivo* study indicates the absence of a significant impact of the co-administration of the MATE1/MATE2K inhibitor pyrimethamine on the PK of gefapixant (gefapixant AUC increase of 24%). At clinically relevant gefapixant concentrations following the proposed dosing regimen of 45 mg BID, no *in vivo* interaction is to be expected via the gefapixant-mediated inhibition of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, BCRP and BSEP. The lack of an interaction via gefapixant-mediated inhibition of OATP1B1/1B3 was confirmed by an *in vivo* interaction with pitavastatin (substrate of OATP1B1/1B3) with ΔCmax and ΔAUC < 10%.

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6.1.4 Pharmacodynamics

Postulated mechanism of action of gefapixant

When the respiratory tract is inflamed, ATP is released from the mucosal cells and this can activate purinergic receptors. Depending on the class, purinergic receptors mediate a large number of different physiological functions. Purinergic receptors of the subtype P2X3R are found mainly in sensory nerve cells, including the sensory C fibres of the vagus nerve. Here purinergic signals are recognised in Schwann cells and can modulate the release of neurotransmitters.

Gefapixant is a P2X3R and P2X2/3R antagonist and probably acts by allosteric modulation. The postulated mechanism of action describes gefapixant as reducing the purinergic stimulation of sensory C fibres and thus reducing cough. This mechanism is new in antitussives.

6.1.5 Secondary Pharmacology (Safety)

Preclinical: No preclinical signals were identified.

Clinical: Two separate gefapixant exposure vs. QTc prolongation analyses were conducted. In one study, single gefapixant doses of up to 1800 mg were administered. 90% confidence intervals for mean ΔΔQTcP remained well below the 10 ms threshold. A second study indicated the absence of a QT/QTc interval prolongation potential following multiple doses of 600 mg BID for 14 days. Also, the categorical analyses in both studies did not reveal effects of gefapixant on the QT/QTc interval.

6.2 Dose Finding and Dose Recommendation

The selection of doses for the Phase 3 studies was based on modelling/simulation of the safety data from all Phase 1 and Phase 2 studies and on the efficacy data from Phase 2 studies.

Study P010 was a dose-escalation study in groups of roughly 30 adult patients with chronic refractory cough per dose. The first cohort was given high doses (50, 100, 150, and 200 mg twice daily), followed by a second cohort given lower doses (7.5, 15, 30, and 50 mg twice daily). Randomised, double-blind, placebo-controlled crossover comparisons of 2 treatment periods lasting 16 days (gefapixant or placebo) were performed for each dose group. The primary endpoint was the awake cough frequency (difference between baseline and post-treatment). The results showed a dose-dependent reduction of cough which may reach peak efficacy at 30 mg.

Study P012 was a randomised, parallel, double-blind, placebo-controlled comparison of groups of roughly 60 adult patients with chronic refractory cough per dose. They were treated with placebo, 7.5 mg, 20 mg, and 50 mg gefapixant twice daily. The primary endpoint was the awake cough frequency after 12 weeks of treatment. Dose-dependent differences were reported in this study too; they only achieved statistical significance for the highest dose. The cough worsened after the treatment was discontinued but did not return to the pre-treatment level.

Both studies reported a dose-dependent increase in taste impairment during treatment with gefapixant.

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6.3 Efficacy

Efficacy was investigated in 2 randomised, placebo-controlled, double-blind, pivotal studies with 1:1:1 parallel-group comparisons of just over 200 (study P027) and just over 400 (study P030) patients per arm (gefapixant 2 x 45 mg versus gefapixant 2 x 15 mg versus placebo).
The studies enrolled adults with either chronic refractory cough (CRC) or unexplained chronic cough (UCC).

The primary endpoints were the reduction of the 24-hour cough frequency versus placebo after 12 weeks of treatment (study P027) and after 24 weeks of treatment (study P030). Both studies were followed by a blinded extension phase (40 weeks in study P027, 28 weeks in study P030).
With respect to the primary endpoints, both studies showed significant differences for gefapixant 45 mg versus placebo (reduction of the 24-hour cough frequency by 18.45% [95% CI: 32.92, 0.86] after 12 weeks and by 14.64% [95% CI: 26.07; 1.43] after 24 weeks) in the primary analysis.

Statistically significant differences between gefapixant 45 mg and placebo were found in all of the sensitivity analyses in study P030, but not in all the sensitivity analyses in study P027.
There were significant differences in the secondary endpoints only in study P030 (reducing awake coughs per hour at Week 24, the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24, the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24).

The submitted pooled subgroup analyses did not describe/show a reversal of this trend for the 2 x 45 mg dose in any of the subpopulations studied.

Efficacy findings from the extension phase of both studies were only submitted for secondary endpoints with no information about the doses given to the patients. The data show numerically better results for gefapixant compared to placebo.

Please refer to the corresponding sections of the Information for healthcare professionals for further information.

The two pivotal studies showed a benefit of gefapixant versus placebo over 12 and 24 weeks for the primary and in some instances also for the secondary endpoints. However, it is difficult to assess the clinical relevance of this effect since there are no established clinical or objective endpoints for assessing cough. The optimum duration of treatment and the length of time for which the treatment effect persists after 24 weeks remain uncertain based on the submitted data.

6.4 Safety

Clinical development comprises a total of 18 Phase 1 studies, 13 Phase 2 studies, and 5 Phase 3 studies, 3 of which are still ongoing. In the Phase 1 studies, a total of 426 people were exposed to the active substance for a maximum of 25 days, in some cases at distinctly supratherapeutic doses. In the Phase 2 studies, a total of 596 people were exposed to the active substance; a total of 1369 people were exposed to gefapixant in the submitted Phase 3 studies, 683 of them to the proposed dose (equivalent to 481 patient-years).
Adverse effects were more frequent on the proposed 45 mg dose of gefapixant. There were no consistent differences between the treatment arms in terms of deaths, other serious adverse events, and laboratory findings.

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In both studies the drop-out rate was substantially higher in patients on 45 mg gefapixant at 22% of patients compared with the rate of 5.8% in those on placebo. The difference between gefapixant 45 mg and the other treatment arms was mainly due to impairment of the sense of taste, although this resolved in 96% of cases by the end of the study. In addition to the increase in adverse effects relating to impaired taste, the studies describe slight imbalances in favour of gefapixant with respect to dry mouth, oral hypaesthesia/paraesthesia, and lower respiratory tract infections, in particular. In nearly one third of the patients, paraesthesia, hypaesthesia and dry mouth did not resolve until after the final dose had been administered.

The signals described above are not prohibitive per se (impaired sense of taste, dry mouth, oral hypaesthesia/paraesthesia, and lower respiratory tract infections).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The pharmacokinetic / pharmacodynamic properties of gefapixant were documented appropriately.

Both pivotal studies describe statistically significantly better results for the primary (reduction of 24-hour cough frequency versus placebo after 12 weeks of treatment (study P027) and after 24 weeks of treatment (study P030)) and to some extent for the secondary endpoints too for the proposed treatment with gefapixant versus placebo. However, the differences to placebo are numerically small and it is difficult to assess their clinical significance.
The possible benefit is opposed primarily by the impairment of taste, which led to about one fifth of the patients given 45 mg gefapixant stopping treatment, even though the impairment resolved in most cases once gefapixant had been discontinued. It is expected that most of the patients who continued taking gefapixant derived a benefit from the treatment. There are some residual uncertainties, particularly concerning possible long-term adverse effects.
Overall, the benefit-risk assessment for patients with chronic refractory cough (CRC) or unexplained chronic cough (UCC) can be considered positive if conventional therapeutic options are not indicated or have not been successful.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Lyfnua was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the Information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Placeholder for text approval stamp

▼ 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 new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Lyfnua®

Composition

Active substances

Gefapixant as gefapixant citrate.

Excipients

Colloidal anhydrous silica, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose and sodium stearyl fumarate. The film coating contains iron oxide red, hypromellose, titanium dioxide, and triacetin. The coated tablets are polished with carnauba wax.
Each 45 mg film-coated tablet contains 0.794 mg sodium.

Pharmaceutical form and active substance quantity per unit

Each film-coated tablet contains 45 mg gefapixant, from 69.48 mg gefapixant citrate. The film-coated tablets are pink, round and convex. Each tablet is debossed with «777» on one side and is plain on the other side.

Indications/Uses

Lyfnua is indicated in adults for the treatment of refractory chronic cough or unexplained chronic cough.

Dosage/Administration

The treatment with Lyfnua should be initiated and monitored by physicians experienced in the management of patients with chronic cough disorders. Prior to the treatment, a work-up of possible underlying cough-causing diseases by a specialized physician must have taken place.

Adult patients

The recommended dosage regimen of Lyfnua in adults is one 45 mg tablet taken orally twice daily with or without food.
Instruct patients that if they miss a dose, they should skip that dose and take the next dose at the regularly scheduled time.

Children and adolescents

Safety and efficacy of Lyfnua have not been established in patients less than 18 years of age.

Elderly patients

No dose adjustment of Lyfnua is required based on age. Of the total number of patients treated with Lyfnua (n=1369) in Phase 3 studies, 476 patients (35%) were 65 years and over, while 94 patients (7%) were 75 years and over. No overall differences in safety or efficacy of Lyfnua were observed with regard to age.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of adverse reactions to this drug may be greater in these patients. Care should be taken with initial dosing frequency (*see Properties/Effects, Pharmacokinetics*).

Patients with hepatic disorders

Lyfnua use has not been studied in patients with hepatic impairment (*see Properties/Effects, Pharmacokinetics*).

Patients with renal disorders

- The recommended dose of Lyfnua in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m^2), not requiring dialysis, is one 45 mg tablet taken once daily with or without food (*see Properties/Effects, Pharmacokinetics*). Insufficient data are available in patients with end-stage renal disease requiring dialysis to make Lyfnua dosing recommendations.
- No dose adjustment is required in patients with mild or moderate renal impairment eGFR ≥30 mL/minute/1.73 m^2.

Increased exposure to gefapixant occurred in patients with renal impairment. The dosage of Lyfnua should be adjusted in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m^2) not requiring dialysis (*see Properties/Effects, Pharmacokinetics*).

Contraindications

Severe hypersensitivity reactions against one of the ingredients.

Warnings and precautions

Hypersensitivity to Sulfonamides

Gefapixant contains a sulfonamide moiety and is considered to be a non-sulfonylarylamine. Gefapixant has not been studied in patients with a history of hypersensitivity to sulfonamide. Lyfnua should be used with caution in patients with known hypersensitivity to sulfonamides.

Obstructive Sleep Apnea

The effect of Lyfnua 45 mg twice daily on oxygen saturation (SaO2) in patients with refractory chronic cough (RCC) or unexplained chronic cough (UCC) with comorbid obstructive sleep apnea (OSA) has not been evaluated.

In a study of patients with moderate to severe OSA (n=19) who were not using positive airway pressure (PAP) and who did not have RCC/UCC, gefapixant 180 mg daily at bedtime (QHS) compared to placebo was associated with a lower mean SaO2 and a higher mean proportion of time with SaO2 <90% across all sleep stages but no difference in the Apnea/Hypopnea Index (AHI), which was the primary endpoint. For patients with RCC/UCC and comorbid OSA, gefapixant should not be used.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablets, that is to say essentially «sodium free».

Interactions

Pharmacokinetic interactions

Potential for Other Drugs to Affect Gefapixant

Metabolism is a minor pathway for gefapixant elimination, and the potential for clinically meaningful drug interactions for gefapixant with co-administration of inhibitors or inducers of cytochrome P450 (CYP) or uridine 5'-diphosphoglucuronic acid glucuronosyl transferase (UGT) enzymes is low.

Concomitant use of a proton pump inhibitor, omeprazole, did not have a clinically meaningful effect on gefapixant pharmacokinetics.

Based on *in vitro* studies, gefapixant is a substrate of efflux transporters multidrug and extrusion protein 1 (MATE1), MATE2K, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). In a Phase 1 clinical trial, a single dose of the MATE1/MATE2K inhibitor pyrimethamine increased gefapixant AUC by 24%, an amount that is not clinically meaningful, and did not affect gefapixant C_{max}.

Potential for Gefapixant to Affect Other Drugs

Based on *in vitro* studies, the potential of gefapixant to cause CYP inhibition or induction is low, and therefore it is unlikely that gefapixant would affect the CYP-mediated metabolism of other drugs.

Gefapixant is an inhibitor of MATE1, MATE2K, organic cation transporter 1 (OCT1), organic anion-transporting polypeptide 1B1 (OATP1B1) and OATP1B3 *in vitro*. However, the risk of clinically meaningful drug interactions via inhibition of these transporters is low for gefapixant administered at 45 mg twice daily. In a Phase 1 clinical trial, multiple doses of gefapixant 45 mg did not affect exposure of the OATP1B substrate pitavastatin.

Effect of Lyfnua on other medicinal products

No clinically meaningful drug interactions have been identified (see *Interactions, Pharmacokinetic interactions*).

Effect of other medicinal products on Lyfnua

No clinically meaningful drug interactions have been identified (see *Interactions, Pharmacokinetic interactions*).

Pregnancy, lactation

Pregnancy

The use of gefapixant in women during pregnancy has not been evaluated. Animal reproduction studies showed no evidence of teratogenicity or embryofetal lethality (see *Preclinical data)*. As a precaution, the use of Lyfnua during pregnancy and in women of childbearing age, who do not use contraception, is not recommended.

Lactation

It is unknown whether gefapixant is present in human milk, affects human milk production, or has effects on the breastfed infant. In animal studies, gefapixant was detected in the milk (see *Preclinical Data*).
A decision must be made whether to discontinue breast-feeding or to discontinue from Lyfnua therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data regarding the effects of Lyfnua on the fertility in humans. Animal studies showed no impairment of fertility (see *Preclinical Data*).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Following administration of gefapixant, dizziness can occur, which can influence the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The safety of gefapixant was evaluated in two Phase III placebo-controlled clinical trials of refractory or unexplained chronic cough, which included a total of 1,369 patients treated with Lyfnua 15 or 45 mg twice daily and 675 patients treated with placebo (see *Clinical Efficacy*). The duration of gefapixant exposure was 52 weeks.
The most frequently reported adverse reactions under treatment with gefapixant 45 mg twice daily were dysgeusia (41 %), ageusia (15 %), and hypogeusia (11 %).

List of adverse reactions

The adverse reactions reported with gefapixant obtained from clinical studies are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as 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), and very rare (< 1/10,000).

Table 1: Adverse Reactions for Lyfnua 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
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, and/or taste salty.	

The majority of patients with taste-related adverse events (dysgeusia, ageusia, hypogeusia and taste disorder) experienced the onset of the adverse event within 9 days of starting Lyfnua; most were mild to moderate in intensity and resolved during treatment or upon discontinuation of Lyfnua. Adverse reactions resulting in discontinuation occurred in 22% of patients receiving Lyfnua. The most frequently reported adverse reactions leading to discontinuation of Lyfnua were dysgeusia (9%) and ageusia (4%).

Description of specific adverse reactions and additional information

Patients treated with 15 mg or 45 mg of gefapixant in the pivotal studies experienced numerically more frequent lower respiratory tract infections, including pneumonia, (5.0% in the 15 mg and 4.2% in the 45 mg group) compared with placebo (3.3%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In a clinical study with 8 healthy subjects administered gefapixant 1800 mg twice daily (40 times the RHD) for up to 14 days, crystals composed of gefapixant were detected in the urine of participants. No evidence of renal or urinary system injury was observed. In case of overdose, monitor the patient for adverse reactions and institute appropriate symptomatic treatment. Gefapixant is partially removed by hemodialysis.

Properties/Effects

ATC code

R05DB29

Mechanism of action

Gefapixant is a selective antagonist of the P2X3 receptor. Gefapixant also has activity against the P2X2/3 receptor subtype. P2X3-containing receptors belong to the family of purinergic receptors and are ATP-gated ion channels found among 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 detected as a damage signal by C fibers and is sensed by the patient as an urge to cough, which in turn, initiates a cough reflex. Gefapixant blocks the ATP mediated activation of P2X3 receptors believed to drive chronic cough, and thus, reduces a patient's cough.

Pharmacodynamics

Cardiac Electrophysiology

The effect of gefapixant on QTc interval was evaluated in a randomized, placebo-controlled single-dose trial in healthy subjects. After a single dose of 1800 mg, which provides at least a 15-fold higher peak concentration than that observed following 45 mg twice daily, Lyfnua does not prolong the QTc interval to a clinically relevant extent.

Clinical efficacy

The efficacy of Lyfnua for the treatment of refractory or unexplained chronic cough was demonstrated in two 52-week, multicenter, randomized, double-blind, placebo-controlled studies of adults with either refractory or unexplained chronic cough. Refractory chronic cough (RCC) was defined as cough associated with a co-morbid condition (e.g., asthma, gastroesophageal reflux disease, or upper airway cough syndrome) that persisted despite adequate treatment of the co-morbid condition. Unexplained

chronic cough (UCC) was defined as cough that was not associated with a co-morbid condition despite a thorough clinical evaluation.

The primary objective of both Phase 3 studies was to demonstrate that Lyfnua was effective in reducing 24-hour cough frequency relative to placebo. Reduction in awake cough frequency and improvement in cough-specific health-related quality of life were secondary objectives. In both studies, patients were randomized to twice daily doses of Lyfnua 45 mg, 15 mg, or placebo. The primary efficacy period for COUGH-1 (NCT03449134) was 12 weeks followed by a blinded extension period of 40 weeks. The primary efficacy period for COUGH-2 (NCT03449147) was 24 weeks, followed by a blinded extension period of 28 weeks.

Patients enrolled in COUGH-1 and COUGH-2 were current nonsmokers, not on ACE-Inhibitors, diagnosed with RCC or UCC, and had chronic cough for greater than 1 year. Most patients were female (75%), white (80%), and from Europe (53%) with a mean age of 58 years (range 19 to 89). A total of 61.5% of patients were diagnosed with RCC, 38.5% with UCC, and the mean duration of chronic cough was 11 years.

Cough Frequency

In COUGH-1 and COUGH-2, patients treated with Lyfnua 45 mg twice daily demonstrated a significant reduction in 24-hour cough frequency compared with placebo (Table 2). The reduction in the 24-hour cough frequency was observed by Week 4 and persisted throughout the primary efficacy period (12 weeks in COUGH-1 and 24 weeks in COUGH-2; Figure 1).

In prespecified pooled analyses of subgroups from both studies at Week 12, the reduction in 24-hour cough frequency for patients treated with Lyfnua 45 mg twice daily, compared with placebo, was not affected by gender, age, region, primary diagnosis, duration of cough, baseline cough severity, or baseline cough frequency (Figure 2).

Table 2: 24-Hour Cough Frequency and Awake Cough Frequency Results for Lyfnua 45 mg BID (COUGH-1 and COUGH-2)

	COUGH-1		**COUGH-2**	
	Lyfnua	**Placebo**	**Lyfnua**	**Placebo**
N	217	222	409	419
24-Hour Cough Frequency (coughs per hour)				
Baseline (geometric mean)	18.24	22.83	18.55	19.48
Week 12 (COUGH-1) or Week 24 (COUGH-2) (geometric mean)	7.05	10.33	6.83	8.34

Week 12 (COUGH-1) or Week 24 (COUGH-2) (%-reduction from baseline)	-61.35	-54.77	-63.17	-57.19
Reduction Relative to Placebo (%-reduction and 95% CI)*	-18.45† (-32.92, -0.86)		-14.64† (-26.07, -1.43)	
Awake Cough Frequency (coughs per hour)				
Baseline (geometric mean)			24.26	25.83
Week 12 (COUGH-1) or Week 24 (COUGH-2) (geometric mean)			8.63	10.82
Week 12 (COUGH-1) or Week 24 (COUGH-2) (%-reduction from baseline)			-64.41	-58.11
Reduction Relative to Placebo (%-reduction and 95% CI)*			-15.79† (-27.27, -2.50)	

N = Number of participants included in the analysis.

CI = Confidence Interval.

* Based on the longitudinal analysis of covariance model using log-transformed cough frequency as dependent variable and including factors for treatment group, visit, the interaction of treatment group by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit as covariates.

† ($p < 0.05$) versus placebo

Figure 1: Analysis of 24-Hour Cough Frequency Over Time for Lyfnua 45 mg BID (COUGH-1 and COUGH-2)

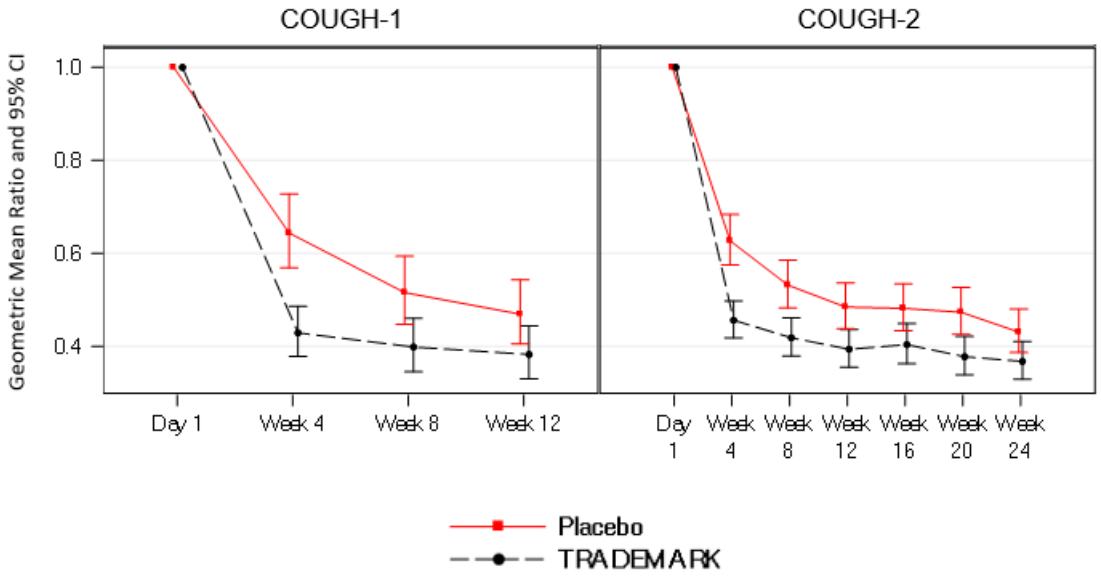
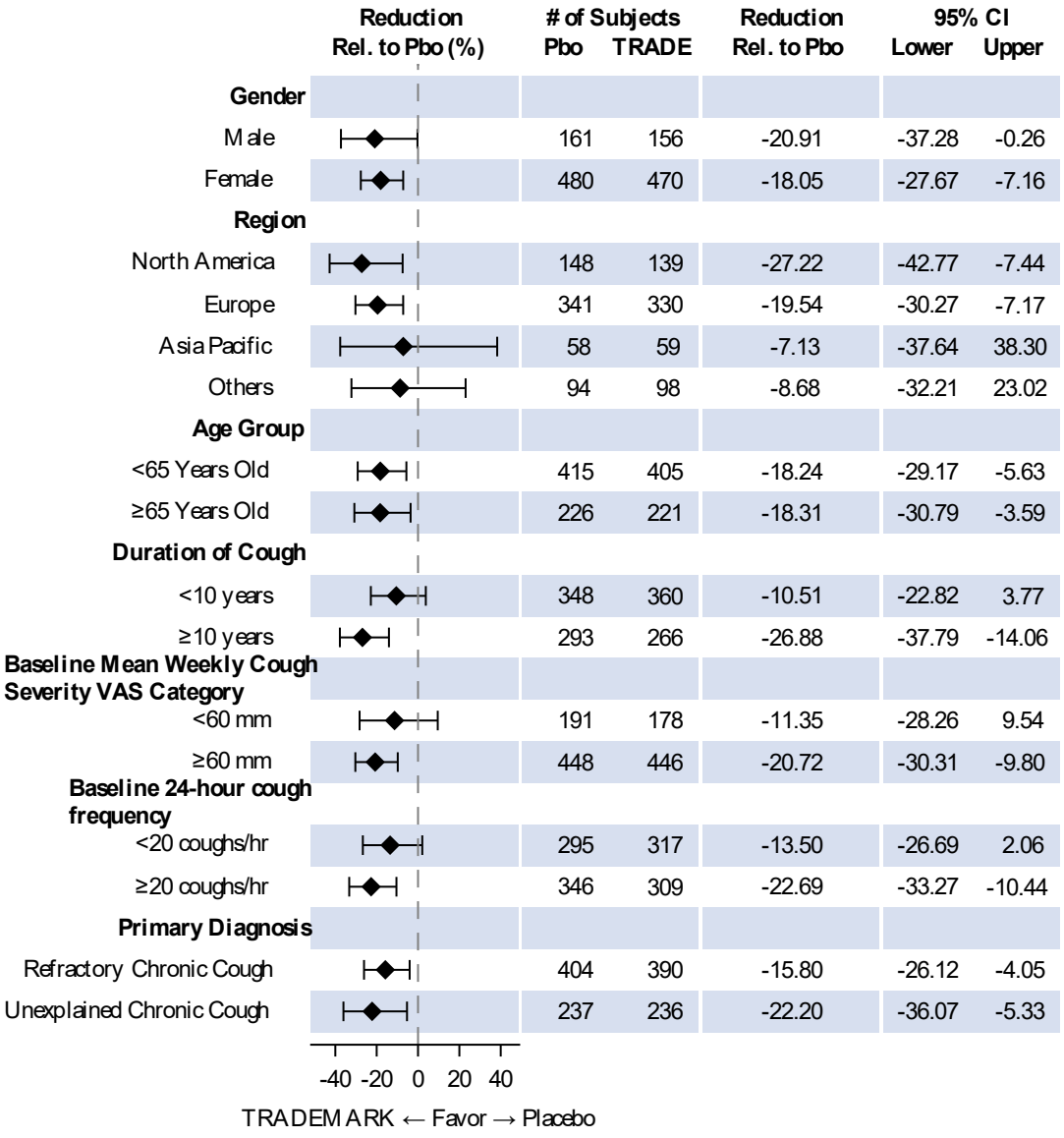


Figure 2: Analysis of 24-Hour Cough Frequency for Lyfnua 45 mg BID at Week 12 by Subgroup for Pooled Phase 3 Studies (COUGH-1 and COUGH-2)



Pbo = placebo

Cough-Specific Health-Related Quality of Life

COUGH-2 was designed to assess also the impact of Lyfnua on cough-specific health-related quality of life relative to placebo as measured by the Leicester Cough Questionnaire (LCQ) (possible score ranges from 3 to 21, with higher scores indicating a better health-related quality of life). In COUGH-2, the odds of having an improvement ≥ 1,3 points in cough-specific health-related quality of life were significantly greater in the Lyfnua 45 mg treatment group than in the placebo group (Table 3).

Table 3: Cough-Specific Health-Related Quality of Life LCQ Results for Lyfnua 45 mg BID (COUGH-2)

	Lyfnua	**Placebo**
N (%)	342 (76.6)	355 (69.0)
Estimated odds ratio vs. placebo (95% CI)*	1.41 (1.02, 1.96)	
p-value*	0.040	

CI = Confidence Interval.
LCQ = Leicester Cough Questionnaire.
N = Number of subjects with available data at Week 24; (%) = Percent responders at Week 24.
* Based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline LCQ total score, and the interaction of baseline LCQ total score by visit.

Pharmacokinetics

The pharmacokinetics of gefapixant were studied in healthy adults and in adults with refractory or unexplained chronic cough and were similar between these two populations. The steady-state mean plasma AUC0-12hr and peak concentration (C_{max}) are 4144 ng·hr/mL and 531 ng/mL with gefapixant 45 mg twice daily treatment. Steady state is achieved within 2 days, with an accumulation ratio of 1.4- to 1.5-fold.

Absorption

Following oral administration of gefapixant, the time to achieve peak plasma concentrations (T_{max}) ranged from 1 to 4 hours. Exposure increases are dose-proportional following multiple doses up to 300 mg twice daily. The fraction absorbed for gefapixant is at least 78%.

Effect of Food

Relative to fasting conditions, oral administration of a single dose of gefapixant 50 mg with a standard high fat and high calorie meal had no effect on the AUC or C_{max} of gefapixant.

Distribution

Based on population pharmacokinetic analyses, the mean steady-state apparent volume of distribution is estimated to be 138 L following oral administration of a 45 mg dose.

In vitro, gefapixant exhibits low plasma protein binding (55%) and has a blood-to-plasma ratio of 1.1. Based on preclinical studies, gefapixant has low CNS penetration.

Metabolism

Metabolism is a minor route of gefapixant elimination, involving oxidation and glucuronidation. Following oral administration of [^{14}C]gefapixant, 14% of the administered dose was recovered as metabolites in the urine and feces. Unchanged gefapixant is the major drug-related component in plasma (87%), and each circulating metabolite accounted for less than 10% of the total radioactivity detected.

Elimination

Renal excretion is the major route of elimination of gefapixant and involves both passive renal filtration and active transport mechanisms. Gefapixant is recovered in urine as parent (~64%) or metabolites (~12%), and the remainder is recovered in feces as parent (~20%) or metabolites (~2%). Active renal secretion is estimated to account for ≤50% of total elimination. Gefapixant has a terminal half-life (t1/2) of 6 – 10 hours.

Kinetics in specific patient groups

Age, gender, race, ethnicity, and body weight do not have a clinically meaningful effect on the pharmacokinetics of gefapixant.

Hepatic impairment

Hepatic metabolism is a minor route of gefapixant elimination; therefore, hepatic impairment is unlikely to have an effect on its exposure.

Renal impairment

Renal excretion is the major route of elimination of gefapixant. Mild or moderate renal impairment (eGFR ≥30 mL/minute/1.73 m^2) does not have a clinically meaningful effect on the exposure of gefapixant.

In a population pharmacokinetic analysis including patients with refractory or unexplained chronic cough, the mean AUC and C_{max} of gefapixant were predicted to increase by 89% and 54%, respectively, in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m^2) compared to those with normal renal function. To maintain similar systemic exposures to those with normal renal function, dosage adjustment is recommended (*see Dosage and Administration, Patients with renal disorders*).

Children and adolescents

No studies with Lyfnua have been performed in patients younger than 18 years of age.

Preclinical data

Repeat Dose Toxicity

Crystalluria occurred in laboratory animals dosed with gefapixant and the majority of the urinary crystals were confirmed to be composed of gefapixant.
In a 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 with 4 times higher exposures than the exposure at RHD of 45 mg twice daily.
In a nine-month, repeat-dose, oral toxicity study in dogs, crystals were observed in the urine at 25, 50 and 100 mg/kg/day. Microscopic findings of focal, minimal tubular degeneration, involving occasional cortical tubules were 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 period. NOAEL for the 9-month dog study was at 50 mg/kg/day with 24 times higher exposures than the exposure at RHD of 45 mg twice daily.

Genotoxicity

Gefapixant was negative in a battery of *in vitro* tests (Ames-test, chromosomal aberration in human peripheral blood lymphocytes) as well as in the *in vivo* rat micronucleus test.

Carcinogenicity

Carcinogenicity studies in rats (2 years in duration) and rasH2 transgenic mice (6 months in duration) with gefapixant showed no evidence of carcinogenic potential (no treatment related tumors) at exposures up to 9 times (rats) and 4 times (mice) the human exposures at the RHD.

Reproductive toxicity

There were no effects on fertility, mating performance or early embryonic development when gefapixant was administered to female and male rats up to the highest dose tested, 675 mg/kg/day (approximately 9 times the AUC in humans at the RHD).
Gefapixant was administered orally to pregnant rats during the period of organogenesis (gestation days (GD) 7-17) at doses of 120, 300 and 675 mg/kg/day. No adverse effects on embryo-fetal development were observed at doses up to 300 mg/kg/day with exposures approximately 6 times the exposure in humans at the RHD. Reduced fetal weights (6-7% relative to controls) were observed at 675 mg/kg/day (approximately 11 times the AUC at the RHD) and were associated with maternal toxicity (decreased food consumption and body weight gain) at this dose.
Gefapixant was administered orally to pregnant rabbits during the period of organogenesis (GD 7-19) at doses of 100, 400 and 1500 mg/kg/day. At a maternally toxic dose (due to decreases in food

consumption, body weight loss and one abortion) of 1500 mg/kg/day (approximately 34-fold the AUC at the RHD), no adverse effect on embryo-fetal development was observed.
Gefapixant was administered orally to rats during pregnancy and lactation period (gestation day 6 to lactation day 20) at doses of 120, 300 and 675 mg/kg/day. At a maternally toxic dose (675 mg/kg/day), (approximately 11-fold the AUC at the RHD), no adverse effects on pre- and postnatal development were observed.
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.
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.

Other information

Shelf life

Do not use this medicinal product after the expiry date («EXP») stated on the pack.

Special precautions for storage

Do not store above 25 °C.
Keep out of the reach of children.

Authorisation number

68065

Packs

Lyfnua 45 mg: 56 and 196 (2x 98) film-coated tablets. [B]

Marketing authorisation holder

MSD MERCK SHARP & DOHME AG
Luzern

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May 2022

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