ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Lyfnua 45 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains gefapixant citrate equivalent to 45 mg of gefapixant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pink, 10 mm, round and convex tablet debossed with "777" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended dose of gefapixant is one 45 mg tablet taken orally twice daily with or without food.

Missed dose
Patients should be instructed that if they miss a dose, they should skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed one.

Special populations

Elderly (≥ 65 years old)
No dose adjustment is required for elderly patients (see sections 5.1 and 5.2).

Gefapixant 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 gefapixant may be greater in these patients. Care should be taken with initial dosing frequency.

Renal impairment
Dose adjustment is required in patients with severe renal impairment (eGFR < 30 mL/minute/1.73 m^2) not requiring dialysis. The dose should be reduced to one 45 mg tablet taken once daily.
No dose adjustment is required in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/minute/1.73 m^2). Insufficient data are available in patients with end-stage renal disease requiring dialysis to make dosing recommendations (see section 5.2).

Hepatic impairment
Patients with hepatic impairment have not been studied. However, given that hepatic metabolism is a minor route of elimination of gefapixant, no dose adjustment is recommended (see section 5.2).

Paediatric population
There is no relevant use of Lyfnua in the paediatric population (under 18 years of age) for the indication of refractory or unexplained chronic cough.

Method of administration

Oral use.
Tablets should be swallowed whole and may be taken with or without food. Patients should be instructed not to break, crush or chew the tablets.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Obstructive sleep apnoea

In patients with moderate to severe obstructive sleep apnoea (OSA, n=19) who were not using positive airway pressure (PAP), gefapixant 180 mg daily at bedtime was associated with a lower mean SaO_2 and a higher mean proportion of time with $SaO_2 < 90\%$ across all sleep stages compared to placebo. The clinical relevance of these findings for the use of 45 mg gefapixant twice daily in patients with refractory chronic cough (RCC) or unexplained chronic cough (UCC) with comorbid OSA is not known. For patients with OSA, appropriate treatment for OSA should be considered prior to initiating treatment with gefapixant.

Hypersensitivity

Gefapixant contains a sulphonamide moiety but is considered to be a non-sulphonylarylamine. Gefapixant has not been studied in patients with a history of hypersensitivity to sulphonamide, therefore, cross-hypersensitivity with sulphonamide hypersensitivity cannot be excluded. Gefapixant should be used with caution in patients with known hypersensitivity to sulphonamides.

Acute lower respiratory tract infection

Treatment with gefapixant should be evaluated and individualised in patients who develop an acute lower respiratory tract infection (see section 5.1).

Taste-related adverse reactions

Taste-related adverse reactions were very commonly reported in the clinical studies. In most patients, these adverse reactions resolved soon after discontinuation of gefapixant (median time 5 days). In a few patients, these reactions persisted for more than a year after discontinuation (see section 4.8).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Based on *in vitro* studies (see section 5.2), relevant clinical interaction studies were performed and no clinically meaningful interactions have been identified.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of gefapixant in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Lyfnua during pregnancy and in women of childbearing potential not using contraception.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of gefapixant in milk (see section 5.3).
A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Lyfnua therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of gefapixant on fertility are available. In rats, there was no effect on mating or fertility with gefapixant treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Gefapixant has no or negligible influence on the ability to drive and use machines. In individual cases, dizziness may occur following administration of gefapixant that may influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were dysgeusia (41%), ageusia (15%), and hypogeusia (11%).

Tabulated list of adverse reactions

The safety of gefapixant was evaluated in two phase III clinical studies (COUGH-1 and COUGH-2) which included a total of 1,369 patients treated with gefapixant (15 mg or 45 mg twice daily) (see section 5.1). The duration of exposure with gefapixant was 52 weeks.

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

System Organ Class	Adverse reactions
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
Psychiatric disorders	
Common	Insomnia
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.

Description of selected adverse reactions

Taste-related adverse reactions
The majority of patients with taste-related adverse reactions (dysgeusia, ageusia, hypogeusia and taste disorder) experienced the onset of the adverse reactions within 9 days of starting gefapixant; the majority were mild (65%) to moderate (32%) in intensity. Resolution of the taste-related adverse reactions occurred in 96% of patients with 25% reporting resolution on or before the last dose of gefapixant. Taste-related adverse reactions persisted for more than a year after discontinuation in 1.6% (7/447) of patients in the gefapixant group and 12.8% (6/47) of patients in the placebo group. Adverse reactions resulting in discontinuation occurred in 22% of patients receiving gefapixant. The most frequently reported adverse reactions leading to discontinuation of treatment were dysgeusia (9%) and ageusia (4%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In a clinical study with 8 healthy subjects administered gefapixant 1,800 mg twice daily (40 times the recommended human dose) 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 cases of overdose reported during the Phase III studies, no adverse events were reported.

In case of overdose, monitor the patient for adverse reactions and institute appropriate supportive measures. Gefapixant is partially removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cough suppressants, 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 receptors are ATP-gated ion channels found on sensory C fibres of the vagus nerve in the airways. C fibres 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 fibres. Activation of C fibres, which is sensed by the patient as an urge to cough, initiates a cough reflex. Blockade of ATP signalling through P2X3 receptors reduces excessive sensory-nerve activation and excessive cough induced by extracellular ATP.

Clinical efficacy and safety

The efficacy of Lyfnua for the treatment of refractory or unexplained chronic cough was studied in two 52-week, multicentre, randomised, 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 III studies was to assess Lyfnua efficacy in reducing 24-hour cough frequency relative to placebo. Reduction in awake cough frequency and cough-specific quality of life were secondary objectives. In both studies, patients were randomised 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 non-smokers, not on angiotensin converting enzyme (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) and 7% of patients were older than 75 years. 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).

The gefapixant 15 mg twice daily group did not demonstrate a significant reduction in 24-hour cough frequency in either study.

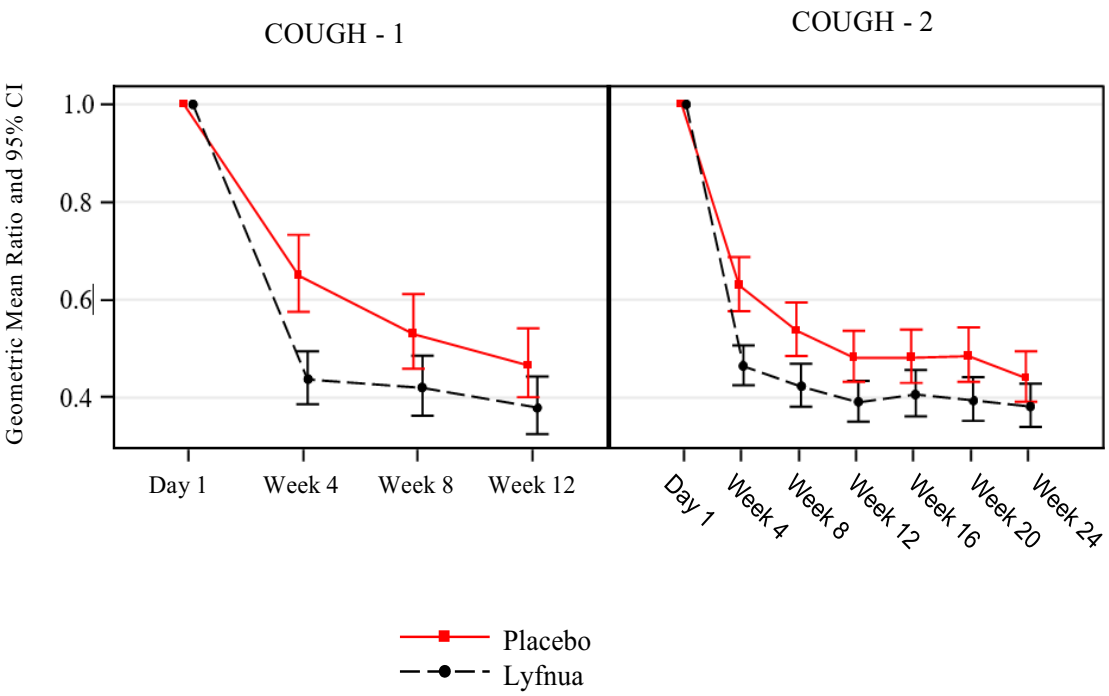
Table 2: 24-hour cough frequency results for Lyfnua 45 mg twice daily (COUGH-1 and COUGH-2)

	COUGH-1		COUGH-2	
	Lyfnua	Placebo	Lyfnua	Placebo
N	243	243	439	435
Primary Efficacy Endpoint				
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)[†]	-18.52 (-32.76, -1.28)		-13.29 (-24.74, -0.10)	
p-value	0.036		0.048	

N = Number of participants included in the analysis. CI = Confidence Interval.

[†]Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed datasets) for all follow-up visits using treatment, gender, region and the other follow-up visits as covariates. Following imputation, an analysis of covariance (ANCOVA) model was conducted at the time point of interest, adjusting for covariates of treatment, baseline, gender, and region.

Figure 1: Analysis of 24-hour cough frequency over time for Lyfnua 45 mg twice daily (COUGH-1 and COUGH-2)



Cough-specific quality of life

COUGH-2 was specifically designed to assess the impact of Lyfnua on cough-specific 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 quality of life). A ≥ 1.3 point increase from baseline in the LCQ total score was defined as clinically meaningful. In COUGH-2, the odds of having a clinically meaningful improvement in cough-specific quality of life were significantly greater in the Lyfnua 45 mg treatment group than in the placebo group as measured at Week 24 (see Table 3).

Table 3: Cough-specific quality of life for Lyfnua 45 mg twice daily (COUGH-2): proportion of patients with ≥ 1.3 point increase from baseline in LCQ total score at Week 24

	Lyfnua	Placebo
N	439	435
Responders* (%)	75.7	68.1
Estimated odds ratio vs. placebo (95% CI)†	1.46 (1.07, 1.99)	
Estimated difference† vs. placebo (95% CI)††	7.63 (1.34, 13.76)	
p-value†	0.016	

N = Number of subjects with available data at Week 24.

* Percent responders at Week 24. Number of responders was calculated by averaging over multiple imputations; there were approximately 332 and 296 responders in Lyfnua and placebo arm, respectively.

CI = Confidence Interval. LCQ = Leicester Cough Questionnaire.

†Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed dataset) for all follow-up visits using treatment, gender, region, and the other follow-up visits as covariates. Following imputation, logistic regression was conducted on the dichotomized scores at the time point of interest, adjusting for covariates of treatment, baseline LCQ total (continuous) score, gender, and region.

††Based on the bootstrap method.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Lyfnua (gefapixant) in all subsets of the paediatric population in treatment of unexplained or chronic refractory cough (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of gefapixant were studied in healthy adults and in adults with RCC or UCC and were similar between these two populations. The steady-state mean plasma AUC and peak concentration (C_{max}) are 4,144 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.

Biotransformation

Hepatic 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 faeces. 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. *In vitro,* gefapixant is a substrate of MATE1, MATE2K, P-gp, and BCRP transporters. Gefapixant has a terminal half-life ($t_{½}$) of 6 – 10 hours.

Special populations

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, dose adjustment is recommended (see section 4.2).

Hepatic impairment
Hepatic metabolism is a minor route of elimination. Most of an oral dose was recovered as unchanged parent in the urine (64%) or faeces (20%). A dedicated study in subjects with hepatic impairment was not conducted, because hepatic impairment is not likely to have a clinically meaningful effect on exposure (see section 4.2).

Effects of age, body weight, gender, ethnicity, and race
Based on a population pharmacokinetic analysis, age, body weight, gender, ethnicity, and race do not have a clinically meaningful effect on the pharmacokinetics of gefapixant.

Drug Interactions

Effects of other medicinal products on the pharmacokinetics of gefapixant
Hepatic 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 toxin extrusion 1 (MATE1), MATE2K, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). In a Phase 1 clinical study, 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}.

Effects of gefapixant on the pharmacokinetics of other medicinal products
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, and 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. The clinical relevance of *in vitro* inhibition of organic cation transporter 1 (OCT1) by gefapixant is not established. In a Phase 1 clinical study, multiple doses of gefapixant 45 mg did not affect exposure of the OATP1B substrate pitavastatin.

5.3 Preclinical safety 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 toxicity study in rats, 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 9 times the exposure in humans at the maximum recommended human dose (MRHD).

In a nine-month repeat-dose oral toxicity study in dogs, crystals were observed in the urine and microscopic observation of focal, minimal tubular degeneration, involving occasional cortical tubules was observed in one male dog at 35 times the exposure in humans at the MRHD.

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 tumours) at exposures up to 9-times (rats) and 4-times (mice) the exposures at the MRHD.

Mutagenesis

Gefapixant was not genotoxic in a battery of *in vitro* or *in vivo* assays including microbial mutagenesis, chromosomal aberration in human peripheral blood lymphocytes and in the *in vivo* rat micronucleus test.

Reproductive toxicity

In animal reproduction studies, oral administration of gefapixant to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity or embryo-fetal lethality at exposures (AUC) that were 6-times (rats) and 34-times (rabbits) the exposure at the MRHD. A slight reduction in rat fetal weights, which was associated with maternal toxicity, was observed at an exposure approximately 11-times the exposure at the MRHD.

Studies in pregnant rats and rabbits showed that gefapixant is transferred to the foetus through the placenta, with foetal 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 9-times the exposure at the MRHD) on lactation day 10, with milk concentrations 4 times that of maternal plasma concentrations observed 1-hour post dose on lactation day 10.
There were no effects on fertility, mating performance or early embryonic development when gefapixant was administered to female and male rats up to 9-times the exposure at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Silica, Collodial Anhydrous (E551)
Crospovidone (E1202)
Hypromellose (E464)
Magnesium stearate (E470b)
Mannitol (E421)
Microcrystalline cellulose (E460)
Sodium stearyl fumarate

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide red (E172)
Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque white PVC/PE/PVdC blisters with push through aluminium lidding foil.
Packs of 28, 56 and 98 film-coated tablets in non-perforated blisters (14 tablets per card) and multipacks containing 196 (2 packs of 98) film-coated tablets in non-perforated blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1613/001
EU/1/21/1613/002
EU/1/21/1613/003
EU/1/21/1613/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lyfnua 45 mg film-coated tablets
gefapixant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 45 mg gefapixant (as citrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
56 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1613/001 (28 film-coated tablets)
EU/1/21/1613/002 (56 film-coated tablets)
EU/1/21/1613/003 (98 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyfnua 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lyfnua 45 mg film-coated tablets
gefapixant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 45 mg gefapixant (as citrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 196 (2 packs of 98) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1613/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyfnua 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lyfnua 45 mg film-coated tablets
gefapixant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 45 mg gefapixant (as citrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1613/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyfnua 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lyfnua 45 mg tablets
gefapixant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lyfnua 45 mg film-coated tablets
gefapixant

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lyfnua is and what it is used for

Lyfnua contains the active substance gefapixant.

Lyfnua is a medicine used in adults for chronic cough (cough that lasts longer than 8 weeks) and:
- the cough does not go away even after using other medicines or
- the reason for the cough is unknown.

The active substance in Lyfnua, gefapixant, blocks the action of nerves that trigger abnormal coughing.

2. What you need to know before you take Lyfnua

Do not take Lyfnua
- if you are **allergic** to gefapixant or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before and while taking Lyfnua if you:
- are **allergic** to medicines containing sulphonamide
- have **sleep apnoea** – where your breathing stops and starts while you sleep
- develop **an acute infection of the lung / lower respiratory system (e.g., pneumonia or bronchitis)**
- experience **change in how things taste, loss of taste,** or **being less able to taste**, that continues even after you stop taking Lyfnua

Children and adolescents
Do not give this medicine to children and adolescents below the age of 18 years. This is because it has not been studied in this age group.

Other medicines and Lyfnua
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
It is not known if Lyfnua can harm your unborn baby. Therefore, it is better to avoid use of Lyfnua if you are pregnant.

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Animal studies have shown that Lyfnua may pass into breast milk. A risk for your baby cannot be excluded. You and your doctor should decide together if you will take Lyfnua or breastfeed.

Driving and using machines
You may feel dizzy after taking Lyfnua. If this happens, do not drive or use tools or machines until you no longer feel dizzy.

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

3. How to take Lyfnua

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose of Lyfnua is:
- one 45 mg tablet twice every day.

Adults with kidney problems
Your doctor may change how much and how often you take Lyfnua if:
- you have severe kidney failure and are not on dialysis.

How to take
Swallow the tablet whole. Do not break, crush, or chew the tablet.
You can take the tablet with or without food.

If you take more Lyfnua than you should
If you take too much Lyfnua, talk to a doctor or pharmacist straight away.

If you forget to take Lyfnua
If you miss a dose, skip that dose and take the next dose at the scheduled time.
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The possible side effects are:

Very common (may affect more than 1 in 10 people)
- change in how things taste (such as a: metallic, bitter, or salty taste)
- being less able to taste
- loss of taste

Common (may affect up to 1 in 10 people)
- feeling sick (nausea)
- things tasting different than before
- cough (worsening, increase)
- dry mouth
- upper respiratory tract infection (an infection in the upper part of the airways including the nose and throat)
- diarrhoea
- pain in your mouth or throat
- feeling less hungry than usual
- feeling dizzy
- upper abdominal (belly) pain
- indigestion
- unusual feeling in mouth (e.g., tingling or prickling sensation)
- loss of feeling in the mouth
- increased saliva production
- insomnia (difficulty in sleeping)

Uncommon (may affect up to 1 in 100 people)
- bladder, urinary or kidney stones

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lyfnua

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the packaging is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lyfnua contains
The active substance is gefapixant. Each film-coated tablet contains 45 mg gefapixant (as citrate). The other ingredients are silica (colloidal anhydrous) (E551), crospovidone (E1202), hypromellose (E464), magnesium stearate (E470b), mannitol (E421), microcrystalline cellulose (E460), sodium stearyl fumarate. The tablets are film-coated with a coating material containing the following ingredients: hypromellose (E464), titanium dioxide (E171), triacetin (E1518) and red ferric oxide (E172). The tablets are polished with carnauba wax (E903).

What Lyfnua looks like and contents of the pack
Lyfnua is a pink, round and convex tablet, debossed with 777 on one side and plain on the other side.

Lyfnua is available in white PVC/PE/PVdC blisters.
Lyfnua is available in packs containing 28, 56 and 98 film-coated tablets in non-perforated blisters (14 tablets per card), multipacks containing 196 (2 packs of 98) film coated tables in non-perforated blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu