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HEALTH TECHNOLOGY BRIEFING
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Gefapixant for chronic refractory cough – First line

NIHRIO ID	7013	**NICE ID**	10267
Developer/Company	Merck Sharp and Dohme Ltd	**UKPS ID**	652193

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Gefapixant is in clinical development for the treatment of refractory or unexplained chronic cough. Cough is a normal reflex response to airway irritation, triggered by stimulation of airway cough receptors, which protect against choking and enhances airway clearance. Chronic refractory cough (defined as a cough lasting more than 8 weeks in adults) collectively refers to chronic cough that fails to respond to treatment of the underlying condition (in cases where an underlying condition has been identified) and unexplained chronic cough where the underlying cause cannot be identified. Current treatment targets the underlying condition and not the cough itself. In cases where there is no underlying condition, many current treatments are used to 'mask' symptoms but with limited effectiveness at treating the cough.

Gefapixant is an oral drug that blocks receptors in the sensory cells in the airways and lungs, potentially reducing cough frequency in patients with refractory or unexplained chronic cough. Preliminary results from early studies have demonstrated that gefapixant is efficacious and safe. If licenced, gefapixant could provide a treatment option for patients with refractory or unexplained cough who have no licensed therapies available and few effective therapies available.

PROPOSED INDICATION

Treatment of refractory or unexplained chronic cough – first line.[1]

TECHNOLOGY

DESCRIPTION

Gefapixant (MK-7264) is a first-in-class, orally administered, non-narcotic therapeutic candidate that selectively inhibits the P2X3 ion channel. It is believed that excessive activation of P2X3 receptors is associated with hyper-sensitisation of sensory neurons. Neuronal hyper-sensitisation in the airways and lungs, triggered by injury or infection, can cause an exaggerated, persistent and frequent urge to cough.[2] By blocking P2X3, gefapixant has reduced cough frequency in patients with refractory or unexplained chronic cough in a phase 2b study.[1]

Gefapixant is currently in clinical development for the treatment of refractory or unexplained chronic cough. In the phase III clinical trials (NCT03449147 and NCT03449134) gefapixant is administered as an oral tablet of 15mg or 45mg, taken twice daily for 52 weeks.[3,4]

INNOVATION AND/OR ADVANTAGES

Current treatment for chronic cough aims at identifying and then treating an underlying condition, such as asthma, and not treatment of the cough itself. This leaves a significant unmet need in patients where the underlying condition is either unknown or the treatment for a known underlying condition is ineffective (the cough is refractory to treatment so could potentially be a comorbidity and have different underlying cause).[5]

Currently there are no licensed treatments for unexplained or refractory chronic cough and a treatment targeting the underlying pathophysiology of this cough will be the first treatment available.

Gefapixant is the first selective antagonist of the P2X3 receptor that has demonstrated efficacy and was generally well-tolerated in phase 2 clinical trials in patients with refractory or unexplained chronic cough.[5,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Gefapixant does not currently have Marketing Authorisation in the EU for any indication.

Gefapixant is in phase II clinical development for endometriosis-related pain.[7]

PATIENT GROUP

DISEASE BACKGROUND

Cough is a protective reflex response to airway irritation. Normally it is triggered by stimulation of airway cough receptors, either by irritants or by conditions that cause airway distortion.[8] Cough involves hypersensitivity of the afferent fibres mediating cough; low levels of stimulation can cause cellular stress releasing adenosine triphosphate (ATP) into the airways, which binds to P2X3 receptors

on afferent neural fibres and is transmitted up to the brainstem then back down to inspiratory and expiratory muscles.[9]

Chronic cough is a cough that lasts eight weeks or longer in adults, or four weeks in children.[10] Patients with the condition cough hundreds or even thousands of times per day; this is similar to the frequency of coughing that occurs in acute viral cough, but chronic cough can persist for months or years.[11]

Patients who have been diagnosed with conditions that are suspected to cause chronic cough (i.e. asthma, gastroesophageal reflux disease (GORD) or non-asthmatic eosinophilic bronchitis), but their cough does not resolve after appropriate treatment of those conditions are considered to have refractory chronic cough. Patients with chronic cough in whom an underlying aetiology cannot be identified are considered to have unexplained chronic cough.[5]

Risk factors for chronic cough can include Angiotensin Converting Enzyme inhibitor (ACE inhibitor) use for high blood pressure, smoking and some occupational exposures/lifestyle changes.[12] Chronic cough is more common among women than among men, most commonly occurs in the fifth and sixth decades of life, and can persist for years with substantial physical, social, and psychological effects.[11]

Chronic cough can lead to a variety of problems including exhaustion, feeling self-conscious, sleep disruption, changes in lifestyle, musculoskeletal pain, hoarseness, and excessive perspiration. Severe cases of chronic cough can cause vomiting, lightheadedness and even rib fractures.[10,13]

CLINICAL NEED AND BURDEN OF DISEASE

A number of different figures for UK chronic cough prevalence have been postulated. A 2006 cross-sectional survey estimated the UK prevalence of chronic cough at 12.0%, while an analysis of CPRD data from a one-year period spanning 2014-15 estimated probable and possible chronic cough prevalence of 0.18% and 1.2% respectively.[14,15] Applying these latter figures to the population estimate in mid-2018 there were potentially 119,584 to 797,226 people with chronic cough in the UK.[16] The proportion of patients within the chronic cough population that have chronic refractory cough is not currently known.

In 2018/19 there were 14,949 hospital admissions with primary diagnosis of cough (ICD-10 code: R05), and 15,927 finished consultant episodes (FCEs), resulting in 6,155 FCE bed days and 3,968 day cases in England.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Patients with chronic refractory or unexplained cough are usually referred to a respiratory physician. A patient presenting with chronic cough (duration >8 weeks) should go through a pathway of examination to identify clinical features of the underlying condition such as Chronic Obstructive Pulmonary Disease (COPD), eosinophilic bronchitis, ACE inhibitor-induced cough or lung cancer. Each condition then has its own treatment pathway.[18]

If the diagnosis is unclear and no cause is identified following initial investigations, sequential trials of treatment for upper airway cough syndrome, asthma and GORD are arranged.[18] If the cough does not respond to the trials of treatment there are no licenced treatments, adults may be offered off-label treatments such as neuromodulators or opioids or non-pharmacological options like cough control therapy.[19]

CURRENT TREATMENT OPTIONS

There are no NICE recommended therapies for the treatment of chronic refractory cough.

The European Respiratory Society recommendations for chronic refractory cough include:[19]

- A trial of low-dose slow-release morphine (5–10 mg twice daily) in adult patients with chronic refractory cough (strong recommendation, moderate-quality evidence).
- A trial of gabapentin or pregabalin in adults with chronic refractory cough (conditional recommendation, low-quality evidence).

PLACE OF TECHNOLOGY

If licensed, gefapixant will offer a first-line treatment option for patients with refractory or unexplained chronic cough who currently have no licensed treatment options and few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**MK-7264-030,** NCT03449147, 2017-003559-49; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants With Chronic Cough **Phase III** **Location(s):** EU (including the UK), Canada, United States and other countries
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled.
Population	N= 1290 (planned); adults aged 18 and over; has had chronic cough for at least 1 year with a diagnosis of refractory chronic cough or unexplained chronic cough.
Intervention(s)	Gefapixant 45 mg or 15 mg tablet administered orally twice daily during the 24-week main study period and during the 28-week extension period.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s): • 24-hour Coughs per Hour at Week 24 • Percentage of Participants Experiencing At Least One Adverse Event (AE) During Treatment and Follow-up [Time Frame: Up to 54 weeks] • Percentage of Participants Who Have a Study Drug Discontinued Due to an AE [Time Frame: Up 52 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**MK-7264-027**, NCT03449134, 2017-000537-31; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants With Chronic Cough **Phase III** **Location(s):** EU (including the UK), Canada, United States and other countries
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled.

Population	N= 720 (planned); adults aged 18 and over; has had chronic cough for at least 1 year with a diagnosis of refractory chronic cough or unexplained chronic cough.
Intervention(s)	Gefapixant 45 mg or 15 mg tablet administered orally twice daily during the main study period (12 weeks) and also during the extension period (40 weeks).
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s): • 24-hour Coughs per Hour at Week 12 • Percentage of Participants Experiencing At Least One Adverse Event (AE) During Treatment and Follow-up [Time Frame: Up to 54 weeks] • Percentage of Participants Who Have a Study Drug Discontinued Due to an AE [Time Frame: Up 52 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**MK-7264-043,** NCT04193202, 2019-002308-42; A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants With Recent Onset Chronic Cough **Phase III** **Location(s):** EU (including the UK), Canada, United States and other countries
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled.
Population	N= 414 (planned); adults aged 18 and over; a diagnosis of refractory chronic cough or unexplained chronic cough (defined as duration of >8 weeks after onset of cough symptoms) for <12 months prior to the screening visit.
Intervention(s)	Gefapixant at a dose of 45 mg administered as an oral tablet twice daily for 12 weeks.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s): • Change from baseline in the Leicester Cough Questionnaire (LCQ) total score at Week 12 [Time Frame: Baseline, Week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**MK-7264-042,** NCT04193176**,** 2019-002321-29; A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Women With Chronic Cough and Stress Urinary Incontinence **Phase III** **Location(s):** EU (including the UK), United States and other countries.
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled.

Population	N= 380 (planned); females aged 18 and over; a diagnosis of refractory chronic cough or unexplained chronic cough; symptoms of Stress Urinary Incontinence.
Intervention(s)	Gefapixant at a dose of 45 mg administered as an oral tablet twice daily for 12 weeks.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s): • Percent change from baseline in average daily cough-induced stress urinary incontinence (SUI) episodes at week 12 [Time frame: baseline, week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of gefapixant is unknown.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Clinical Knowledge Summary. Scenario: Management - cough more than 8 weeks' duration. 2015

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Ribas CD, et al. European Respiratory Society guidelines on the diagnosis and treatment of chronic cough in adults and children. 2020.[19]
- Irwin RS, Baumann MH, Bolser DC, Boulet L-P, Braman SS, Brightling CE, et al. Diagnosis and Management of Cough Executive Summary– ACCP Evidence-Based Clinical Practice Guideline. 2006.[20]
- Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. *British Thoracic Society Cough Guideline Group.* 2006.[12]

ADDITIONAL INFORMATION

REFERENCES

1 Smith JA, Kitt MM, Morice AH, Birring SS, McGarvey LP, Sher MR, et al. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. *The Lancet Respiratory Medicine*. 2020 2020/02/25/. Available from: https://doi.org/10.1016/S2213-2600(19)30471-0.

2 Merck. *Merck Announces Presentation of Phase 2 Results for MK-7264, an Investigational, P2X3 Receptor Antagonist, Being Evaluated for the Treatment of Chronic Cough.* 2017. Available from: https://www.mrknewsroom.com/news-release/research-and-development-news/merck-announces-presentation-phase-2-results-mk-7264-inve [Accessed 16 Jan 2020].

3 Clinicaltrials.gov. *A Study of Gefapixant (MK-7264) in Adult Participants With Chronic Cough*. *Trial ID: NCT03449147*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03449147 [Accessed 16 Jan 2020].

4 Clinicaltrials.gov. *Phase 3 Study of Gefapixant (MK-7264) in Adult Participants With Chronic Cough (MK-7264-027)*. *Trial ID: NCT03449134*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03449134 [Accessed 16 Jan 2020].

5 Muccino D, Green S. Update on the clinical development of gefapixant, a P2X3 receptor antagonist for the treatment of refractory chronic cough. *Pulmonary Pharmacology & Therapeutics*. 2019;56:75-8. Available from: https://doi.org/10.1016/j.pupt.2019.03.006.

6 Pulmonology Advisor. *Gefapixant Improves Quality of Life and Cough Frequency in Chronic Cough.* 2019. Available from: https://www.pulmonologyadvisor.com/home/meetings/chest-2019/cough-frequency-and-quality-of-life-improved-in-chronic-cough-with-gefapixant/ [Accessed 22 Jan 2020].

7 Clinicaltrials.gov. *Search: "Gefapixant | Phase 2, 3".* 2020. Available from: https://clinicaltrials.gov/ct2/results?term=Gefapixant&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 16 Jan 2020].

8 National Institute for Health and Care Excellence. *Clinical Knowledge Summaries: Cough.* 2015. Available from: https://cks.nice.org.uk/cough#!topicSummary [Accessed 07 Feb 2020].

9 Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *European Respiratory Journal*. 2020;55(1):1901136. Available from: https://doi.org/10.1183/13993003.01136-2019.

10 Mayo Clinic. *Chronic Cough.* Available from: https://www.mayoclinic.org/diseases-conditions/chronic-cough/symptoms-causes/syc-20351575 [Accessed 17 Jan 2020].

11 Smith JA, Woodcock A. Chronic Cough. *New England Journal of Medicine*. 2016;375(16):1544-51. Available from: https://doi.org/10.1056/NEJMcp1414215.

12 Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. *Thorax*. 2006;61(suppl 1):i1. Available from: https://doi.org/10.1136/thx.2006.065144.

13 Agency for Healthcare Research and Quality. *Assessment and Management of Chronic Cough.* 2012. Available from: https://effectivehealthcare.ahrq.gov/products/chronic-cough/research-protocol [Accessed 23 Jan 2020].

14 Ford AC, Forman D, Moayyedi P, Morice AH. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax*. 2006;61(11):975. Available from: https://doi.org/10.1136/thx.2006.060087.

15 Holden SE, Morice A, Birring SS, Jenkins-Jones S, Langerman H, Weaver J, et al. Cough presentation in primary care and the identification of chronic cough: a need for diagnostic clarity? *Current medical research and opinion*. 2020 2020/01/02;36(1):139-50. Available from: https://doi.org/10.1080/03007995.2019.1673716.

16 Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2018*. Available from: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland/mid20182019laboundaries/ukmidyearestimates20182019ladcodes.xls

17 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

18 National institute for Health and Care Excellence. *Clinical knowledge summaries: Scenario: Management - cough more than 8 weeks' duration.* 2015. Available from: https://cks.nice.org.uk/cough#!scenario:2 [Accessed 21 Jan 2020].

19 Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Ribas CD, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *European Respiratory Journal*. 2019:1901136. Available from: https://doi.org/10.1183/13993003.01136-2019.

20 Irwin RS, Baumann MH, Bolser DC, Boulet L-P, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 Suppl):1S-23S. Available from: https://doi.org/10.1378/chest.129.1_suppl.1S.

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