HANDBOOK

This handbook was developed and funded by Pfizer

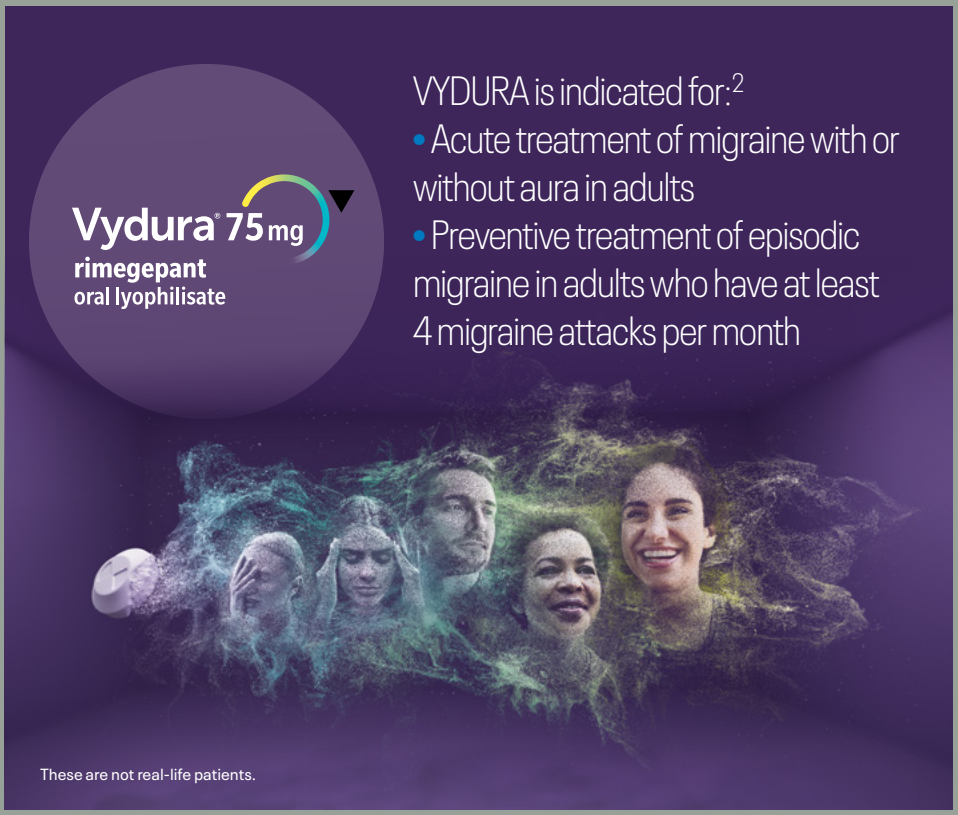
Produced in collaboration with Cogora.

PULSE

Intended for UK healthcare professionals only. Prescribing information and Adverse Event Reporting Information for VYDURA®▼(rimegepant) for GB and NI can be found on page 27.

Many migraine needs: take a targeted approach[1,2]

The possibility of acute treatment of migraine or preventative treatment of episodic migraine in adults with VYDURA®



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Foreword

Katy Munro
GP with a Special Interest in Headache, National Migraine Centre

Migraine is one of the most common conditions and the second most disabling condition, globally.[1,2] One in seven of us suffer from migraine but often the diagnosis goes unrecognised by patients or healthcare professionals, and thus management may not be suitable.[1] Many sufferers are women of reproductive age with multiple roles including work, partner, parent, carer; one in three women have migraine.[1] Fluctuations in hormones throughout a woman's life often contribute to exacerbations.[3]

It's not just about headache, however; problems with your sight, numbness, feeling dizzy and difficulty speaking are just a few symptoms commonly described by people having migraine attacks.[4] Societally, a condition which is dismissed, stigmatised and misunderstood, there is a lack of training about migraine for healthcare professionals too.[5] Repeated attendances in primary care or at A&E departments may result in frustrated patients, overloaded waiting rooms and unnecessary referrals to secondary care; leaving clinicians scratching their heads for the next treatment option.[5]

The impact of migraine on a person's family, friends, and work or school lives may be very costly both in human terms of lost opportunities and economic terms. The risk of over-using acute painkillers and triptans leading to "medication overuse headache" is real.[6] Although that term is disliked by many headache specialists, we see desperate patients who have developed this chronic background and experience daily pain; having not been warned about the golden rule of only using acute analgesics and triptans on a maximum of 10 days per month, and avoiding codeine and opioids completely, if possible.[6]

As a Headache Specialist General Practitioner (GP) who previously worked as an NHS GP partner for 25 years, I recognise the difficulties faced by GPs trying to manage this complex, neurological condition. History-taking is key to the diagnosis and the recognition of the impact on the patient. In my work for the National Migraine Centre charity, I have the luxury of much longer appointment times. Management plans should include lifestyle advice, rescue treatment guidance about which medications to take and when, and a discussion around the now numerous choices for both acute and preventive treatments.

There are several obstacles to optimal migraine management. People with mild or infrequent attacks may not seek help, not realising how much is available to reduce the impact. Migraine may be misdiagnosed as tension headache, sinusitis, Meniere's disease, dental issues or 'just a normal headache' (a particularly misleading term – headache is a symptom requiring a diagnosis).[7-9] Sufferers may be advised on unhelpful strategies such

as 'Just manage your stress better', 'Drink more water', 'Do more exercise' or even, 'Have a baby' or 'Wait until you go through menopause, that will help'.

Once the diagnosis is made, it is also helpful to discuss lifestyle strategies.[10] As a clinician, it's important to know the kind of impact and the different scenarios where migraine exacerbations occur; for example, around menstruation, after exercise, when sleep is broken or meals are skipped.[10] Looking ahead to the future – understanding plans for pregnancy, starting a new job or college course, travel plans – requires a personalised treatment plan approach. Attacks may change with age; the most bothersome symptom may subside or develop anew.[11]

Until recently, all the preventive migraine medications have been borrowed from other conditions and can have troublesome side effects, reducing efficacy and concordance. Rimegepant offers a paradigm shift in the way we manage migraine. Developed specifically to block one of the neurochemicals, calcitonin gene-related peptide (CGRP), receptor, it is licensed for the treatment of acute migraine with or without aura, or the preventive treatment of episodic migraine.[12-14] An oral lyophilisate, it is easier for the patient compared to subcutaneous or intravenous monoclonal antibodies, and has no data to suggest it can induce medication overuse headache (although safety data is still being collected).[12,15]

In many, migraine improves with age, but this is by no means universal.[11]

With the availability of medications developed specifically to target one of the migraine-triggering neurochemicals, the time is right for migraine management to be much higher on the agenda of commissioners.

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Introduction

Migraine is the most common severe form of primary headache with no associated underlying pathology.[3,4] It occurs in 15% of the UK adult population and is 3 times more common in females than in males.[4] Migraine is the second leading cause of years lived with disability.[5] In the UK alone, 3 million workdays are lost every year to migraine-related absenteeism, at a cost of almost £4.4 billion; despite this, it is still underdiagnosed and undertreated.[5,6]

VYDURA (rimegepant) is a calcitonin gene-related peptide (CGRP) receptor antagonist indicated for the acute treatment of migraine with or without aura in adults; or the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month.[2]

Abbreviations

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CLcr	Creatinine clearance
C_{max}	Peak plasma concentration
CYP3A4	Cytochrome P450 3A4
DALY	Disability-adjusted life years
ECG	Electrocardiogram
ICHD	International Classification of Headache Disorders
MBS	Most bothersome symptom
MIDAS	Migraine Disability Assessment
MMD	Monthly migraine days
MOH	Medication overuse headache
MSQ	Migraine-Specific Quality-of-Life Questionnaire
NSAID	Non-steroidal anti-inflammatory drug
P-gp	P-glycoprotein
QOL	Quality of life
SD	Standard deviation
STS	Sheehan Suicidality Tracking Scale
ULN	Upper limit of normal

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Meet Preeti, a patient with migraine with aura

Case study (not a real patient); full case study on page 25.

Not a real patient, for illustrative purposes only

Preeti is 31 years old and works as a clinical biochemist. Preeti's migraines include a unilateral headache in the forehead with severe pain, nausea, photophobia, and visual aura. Preeti's migraines are exacerbated by stress, as well as certain foods and drinks. Despite medication previously proving effective, her attacks now interrupt her work and have increased her number of sick days.

History 6+ years of migraine
Migraine type Acute with aura (3 to 4 moderate-to-severe migraines/month)
Current treatment Oral triptan; oral non-steroidal anti-inflammatory drug (NSAID) when required
Previous treatment Oral paracetamol when needed; 1 alternative oral triptans

The many types of migraine

VYDURA is indicated for the acute treatment of migraine with or without aura in adults, or for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month.

There are many different types of migraine, so not all patients presenting with migraine in primary care will have a 'typical' diagnosis.

Migraine with and without aura
Aura is characterised as reversible, transient focal neurological symptoms arising from the cortex or brainstem.[7]

There is a large variation in the presentation of aura both between patients and from 1 attack to another; many patients may experience attacks both with and without aura.[7] Headache must not be better accounted for by another diagnosis.[8]

Figure 1. Diagnostic criteria for migraine with and without aura[8]

Migraine with aura, presenting with at least 2 attacks including one or more of:[8]

- Visual symptoms such as zigzag lines and/or scotoma — visual aura is the most common type of aura
- Sensory symptoms such as unilateral pins and needles or numbness
- Speech and/or language symptoms such as dysphasia

At least 3 of the following:[8]

- At least 1 aura symptom spreads gradually over at least 5 minutes
- 2 or more aura symptoms occur in succession
- Each individual aura symptom lasts 5 to 60 minutes
- At least 1 aura symptom is unilateral
- At least 1 aura symptom is positive
- The aura is accompanied, or followed within 60 minutes, by headache

Migraine without aura, presenting with at least 5 headaches, lasting 4 to 72 hours, including 2 or more of the following characteristics:[8]

- Unilateral location
- Pulsating quality — may be described as 'throbbing' or 'banging' in young people
- Moderate or severe pain intensity
- Aggravation by, or causing avoidance of, routine activities of daily life (for example, walking or climbing stairs)

Headache with associated symptoms including at least 1 of:[8]

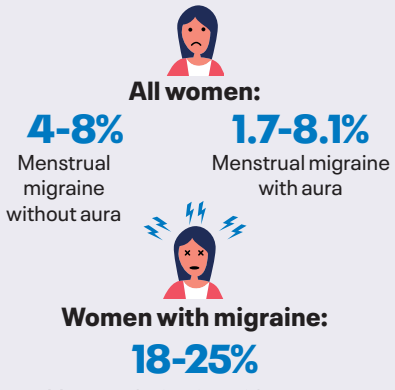
- Nausea and/or vomiting
- Photophobia (sensitivity to light) and phonophobia (sensitivity to sound)

VYDURA is indicated for the acute treatment of migraine with or without aura in adults, or for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month.

Episodic migraine vs. chronic migraine
Episodic migraine can be diagnosed in people presenting with migraine occurring on less than 15 days per month.[8] Alternatively, chronic migraine can be diagnosed in people presenting with headache occurring on at least 15 days per month (with features of migraine on at least 8 days per month) for more than 3 months.[8] Headache must not be better accounted for by another diagnosis.[8]

Menstrual-related migraine
Menstrual-related migraine should be suspected in women or girls with migraine occurring predominantly between 2 days before and 3 days after the start of menstruation for at least 2/3 consecutive menstrual cycles.[8]

Figure 2. Prevalence of menstrual-related migraine[9]



There is difficulty with diagnosing menstrual migraine due to lack of clarity on the critical timeframe around menstruation.[9]

Vestibular migraine
Vestibular migraine is characterised by recurrent vestibular attacks, often accompanied by migraine headaches and other migraine symptoms.[10] Features of vestibular attacks include ataxia, visual disorders, occipital pressure, nausea and vomiting.[11] It is thought to affect 1% to 3% of the general population and 10% to 30% of patients experiencing dizziness.[10]

Figure 3. Patient analogies for vestibular migraine to look out for[12]

Importance of effective migraine treatment

Migraine is a common condition with a global prevalence of around 1 in 7 people.[13] Migraine is 2-to-3 times more common in women than men, with a lifetime prevalence of 33% in women and 13% in men.[13]

In the UK alone, migraine is estimated to cost around £3 billion a year in direct and indirect costs when considering costs of healthcare, lost productivity, and disability.[4]

Not a real patient, for illustrative purposes only

Underdiagnosis and undertreatment in Europe

People with headache are underdiagnosed and undertreated, not only in poorer countries with limited resources but also across Europe and North America.[6] Research into a UK population with migraine (N=49) identified that 44.9% (n=22) of the study sample were experiencing ≥5 monthly migraine days (MMDs) and yet, of this group, 9.1% (n=2) were using a preventive medication.[6]

Survey data, published in 2018, reported that 24.5% (n=12) of the UK population with migraine were receiving triptans for the treatment of acute migraine.[6] It is estimated that sustained freedom from pain is achieved in 18% to 33% of patients following standard dose triptans (freedom from pain at 24 hours was calculated based on 42 studies and a total of 27,755 participants. Included studies were published between 1991 and 2012. Overall, 20 different treatments were considered, involving 115 comparisons).[6,14,15]

Impact on patient quality of life

The common themes of concern in migraine patients are disease condition, quality of life (QOL) and health status, and negative social response.[16] Worsened patient QOL and greater risk of anxiety and depression is associated with a higher frequency of headaches.[17] The unpredictability of migraine attacks and the fear of inducing an attack can create anxiety and make it difficult for people with migraine to reliably plan their work and attend outings.[18]

Migraine-related productivity loss

Migraine is the second leading cause of years lived with disability.[5]

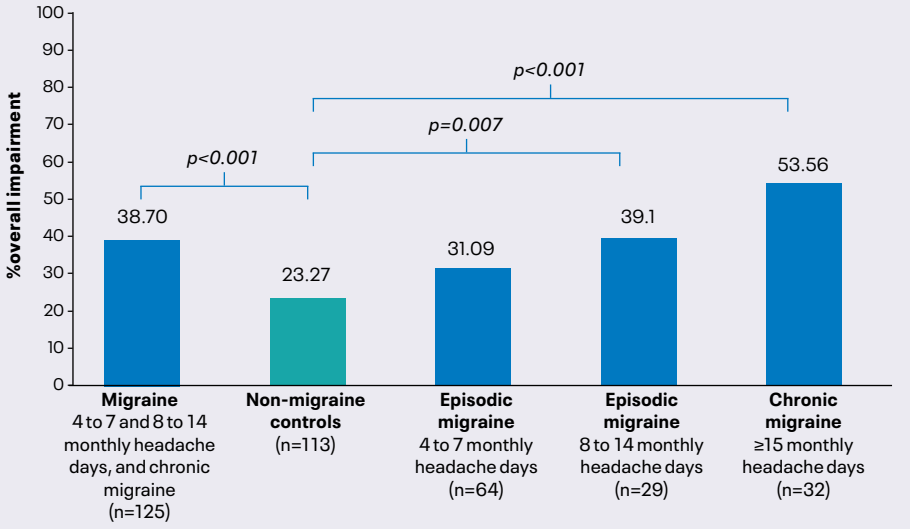
3 million workdays are lost every year to migraine-related absenteeism, at a cost of almost £4.4 billion.[5] In the 'My Migraine Voice Survey', which aimed to understand views on people with migraine across 31 countries (N=11,266; mean time affected by migraine, 11.6 years; 76% taking acute medication), 70% reported that migraine

had affected their professional life.[18] The top 3 impacts of migraine on work reported by the respondents were inability to concentrate on work (52%), missing too many days work (32%) and a lack of understanding among their colleagues about their condition or taking it seriously (27%).[18]

In the UK, 100,000 people are absent from work or school due to migraine every working day.[4] Survey data in France, Germany, Italy, Spain, and the UK showed that people with migraine reported significantly higher absenteeism (14.4% vs 9.5%, respectively; p=0.001) and impairment while at work (35.5% vs 21.0%, respectively; p<0.001) compared to people without migraine.[19] Health resource utilisation (HRU) was also significantly higher in people with migraine compared to people without migraine samples due to more healthcare professional and emergency visits.[19]

Higher incremental impairment while at work in people with migraine vs non-migraine controls were noted across the migraine sample irrespective of migraine frequency.[19]

Figure 4. Total work productivity impairment in migraine subgroups vs propensity score matched non-migraine controls. Mann-Whitney tests were used for analysis[19]



Adapted from Vo *et al.* 2018[19]. VYDURA is indicated for the acute treatment of migraine with or without aura in adults, or for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month.

Introduction to VYDURA

VYDURA is an oral lyophilisate containing rimegepant sulphate, equivalent to 75mg rimegepant.[2] The oral lyophilisate should be placed on or under the tongue; it will disintegrate in the mouth and can be taken without liquid.[2]

Figure 5. VYDURA indications:[2]

Acute treatment of migraine with or without aura in adults

or

Preventive treatment of episodic migraine in adults who have at least four migraine attacks per month

VYDURA is a CGRP receptor antagonist.[2] CGRP is a pain-signalling neuropeptide that plays a causative role in migraine.[20,21] **VYDURA selectively binds with high affinity to the CGRP receptor, thereby antagonising its function.[2] The relationship between pharmacodynamic activity and the mechanism(s) by which VYDURA exerts its clinical effects is unknown.[2]**

Figure 6 and 7. Mode of action of CGRP receptor antagonists [23]

CGRP receptor antagonists work by:
Figure 6: Inhibiting exaggerated pain signalling[23]

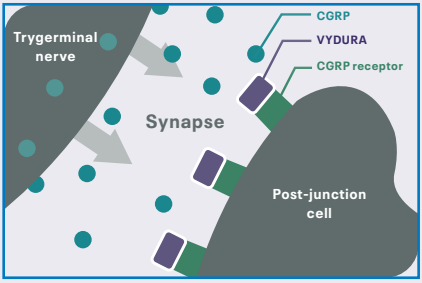
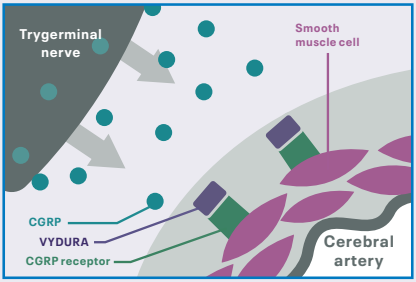


Figure 7: Inhibiting vasodilation without active vasoconstriction[20,22]



(Adapted from Durham 2004[23])

Medication overuse headache

Patients with migraine are particularly susceptible to medication overuse headache (MOH).[24] MOH is a secondary headache disorder with an estimated prevalence of 1% to 3% of the general population worldwide.[24,25] Patients with MOH and migraine have a greater likelihood of hospitalisation and 57% higher annual healthcare costs than patients with migraine alone.[26]

MOH involves elements of chronic pain and substance misuse, both of which have been linked to suicide risk.[27]

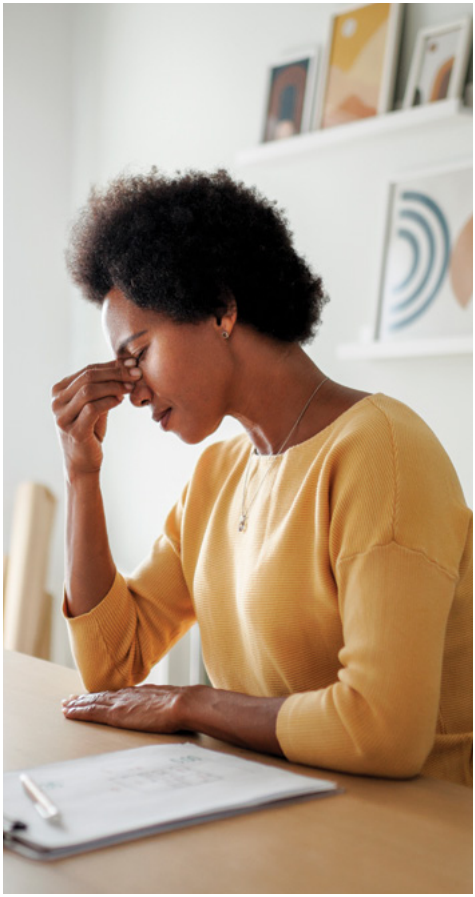
MOH is defined as:[25]

- Headache occurring 15 or more days per month
- Use of triptans, opioids, ergots, barbiturates, or a combination of these on ≥10 days per month
- Use of aspirin, NSAIDs, or paracetamol on ≥15 days per month
- The pathogenesis of MOH can likely be a consequence of upregulation of the CGRP system.[24] Simple analgesics, such as paracetamol or NSAIDs, and opioids have the highest rates of MOH, followed by triptans.[28]

What is the MOH risk profile of CGRP receptor antagonists?

Currently, there are **no data** suggesting that chronic blockage of the CGRP receptor can induce MOH, although long-term effects of CGRP receptor-blocking agents should be studied.[29] However, overuse of any type of medicinal product for headaches can make them worse.[2] If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued.[2]

The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of medicinal products for acute headache.[2]



Not a real patient, for illustrative purposes only

Rimegepant for the acute treatment of migraine (Study 303)

The efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine was assessed in a randomised, phase 3, double-blind, placebo-controlled trial at 69 sites across the USA.[2,30]

Screened patients were entered into an interactive web response system and returned to study centres within 3 to 28 days of signing informed consent.[30] Participants were randomly assigned in a 1:1 ratio to either rimegepant (n=732) or placebo (n=734) for treatment of a single migraine attack of moderate or severe pain intensity and provided with an electronic diary.[30]

Inclusion criteria[30]	Exclusion criteria[30]
• Adults aged ≥18 years • ≥1 year history of migraine with or without aura, according to the criteria of the 3rd Edition of International Classification of Headache Disorders (ICHD) beta version • Onset before 50 years of age • ≥2 but ≤8 migraine attacks/month of moderate-to-severe intensity • <15 days/month with migraine/non-migraine headache within the past 3 months	• Have a medical condition that may interfere with study assessments • Been treated for drug or alcohol abuse in the past 12 months • Had a history of drug allergy or other allergy that made them unsuitable for participation • Had an electrocardiogram (ECG) or laboratory test findings that raised safety or tolerability concerns

This study included only the use of NSAIDs, paracetamol, antiemetics or baclofen, within 24 hours post dose; the use of triptans or other acute migraine medication was not allowed. This study was conducted using orally disintegrating tablet formulation of rimegepant 75 mg; the formulation of VYDURA used within the UK is oral lyophilisate 75mg.[30]

Co-primary and secondary endpoints

The co-primary endpoints were **freedom from headache pain at 2 hours post dose**, defined as a reduction in headache severity from moderate/severe at baseline to no pain; and **freedom from most bothersome symptom (MBS) at 2 hours post dose**, defined as the absence of the self-identified MBS (common MBS included photophobia, nausea and phonophobia).[30]

Hierarchical Gate Keeping

To control the type I statistical error rate at 0·05, a hierarchical gate-keeping procedure was applied, with a prespecified sequence of comparisons from the coprimary endpoints through the secondary endpoints in the order listed in the protocol.[30]

Scan the QR code for the complete list of hierarchal endpoints:
(This link takes you to a promotional website developed and funded by Pfizer Ltd.)

Categories	2-hour post-dose endpoints[30]	90-min and 60-min post-dose endpoints[30]	2h-24h and 24h-48h post-dose 'sustained' effects endpoints[30]
Secondary endpoints[30]	• Pain relief, freedom from photophobia, freedom from phonophobia, freedom from nausea and ability to function normally at 2 hours	• Freedom from pain at 90 min, freedom from MBS at 90 min • At 60 and 90 minutes post dose: pain relief and ability to function normally	• At 2 to 24 hours and 2 to 48 hours post dose: sustained freedom from pain, sustained freedom from MBS, sustained pain relief and sustained ability to function normally • Use of rescue medication within 24 hours of dose Pain relapse 2 to 48 hours post dose

Table 1: Secondary endpoints by category for Study 303[30]

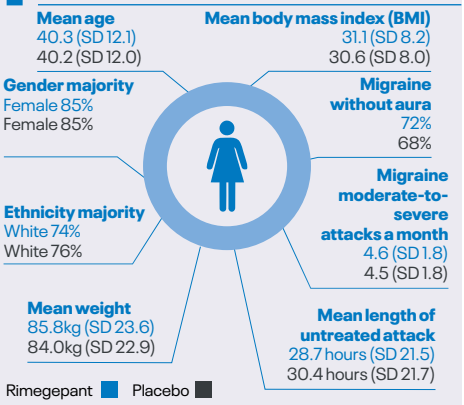
The safety and tolerability endpoints measured in this trial included adverse events (AE); ECG, vital signs, physical measurements; routine laboratory tests; Sheehan Suicidality Tracking Scale* (STS).[30]

End point definitions[30]

- Pain intensity was measured on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe). Pain relief was also measured using this scale
- The MBS (nausea, phonophobia or photophobia) was measured using a binary scale (0=absent, 1=present)
- Ability to function normally was measured on a four-point scale (normal function, mild impairment, severe impairment, or required bedrest)
- The probability of using rescue medication was calculated on the basis of the number of participants in the group who reported using such medications

*The Sheehan STS is a prospective, subjects self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviours

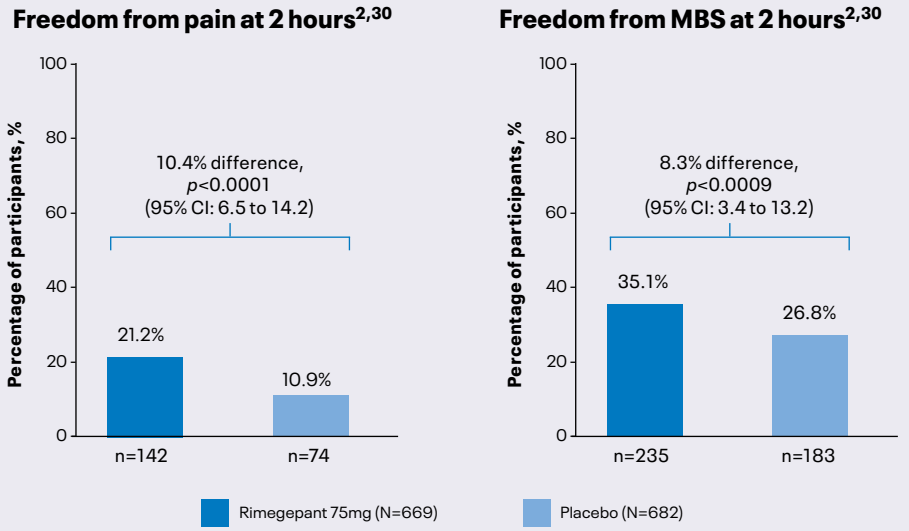
Figure 8. Baseline characteristics (N=1,351)[30]



Rimegepant for the acute treatment of migraine (Study 303)

Figure 9. Rimegepant was statistically significantly more effective than placebo on the co-primary efficacy endpoints of freedom from pain and MBS at 2 hours post dose[30]

Percentage of patients experienced freedom from pain at 2 hours and freedom from MBS at 2 hours when receiving rimegepant, as compared with placebo[30]



The secondary endpoints are numbered from 1 to 21 in order of hierarchal testing. Rimegepant was statistically significantly more effective than placebo on 19 out of 21 endpoints, including:[30]

- Pain relief post dose (secondary endpoints 1 & 18); at 2 hours (59.3% vs. 43.3%; risk difference 16.1; 95% CI 10.8-21.3) and 60 minutes (36.8% vs. 31.2%; risk difference 5.5; 95% CI 0.5-10.6)[2,30]
- Ability to function normally post dose (secondary endpoints 2 & 19); at 2 hours (38.1% vs. 25.8%; risk difference 12.3; 95% CI 7.4-17.2) and 60 minutes (22.3% vs. 15.8%; risk difference 6.4; 95% CI 2.3-10.6)[2,30]
- Sustained pain relief from 2 to 48 hours post dose (42.2% vs. 25.2%; risk difference 16.9; 95% CI 12.0-21.9)[30]
- No rescue medication in the first 24 hours (85.8% vs. 70.8%; risk difference 15.0; 95% CI 10.7-19.3)[30]

Not a real patient, for illustrative purposes only

	Rimegepant 75 mg (n=682)[30]	Placebo (n=693)[30]
Participants with AEs	90 (13%)	73 (11%)
AEs reported in ≥1% of participants in either treatment group		
Nausea	11 (2%)	3 (<1%)
Urinary tract infection	10 (1%)	4 (1%)
Dizziness	6 (1%)	7 (1%)
AEs related to treatment	47 (7%)	36 (5%)
Serious AEs	0	0

Table 2: Adverse events reporting in Study 303[30]

No participants in either group had elevations of bilirubin >2x upper limit of normal (ULN), 1 participant per group had a transaminase concentration >3x ULN, although neither were attributed to study medication.[30]

Rimegepant for the prevention of episodic migraine (Study 305)

The efficacy, safety, and tolerability of rimegepant for the preventive treatment of migraine was assessed by a multicentre, phase 2/3, randomised, double-blind, placebo-controlled trial at 92 sites in the USA.[31]

Over a 4-week observation phase, the occurrence and severity of migraine and medication used was recorded and served as baseline headache occurrence.[31] The study comprised 3 phases: a screening phase, which included a 4-week observation period, a 12-week double-blind treatment phase, and a 52-week open-label extension phase.[31] At the baseline visit, eligible participants were randomly allocated in a 1:1 ratio to either rimegepant (n=373) or placebo (n=374).[31]

Inclusion criteria[31]	Exclusion criteria[31]
• Adults aged ≥18 years • ≥1 year history of migraine with or without aura, or chronic migraine, according to the criteria of the ICHD, 3rd Edition • Onset before 50 years of age • At least 4 but ≤18 migraine attacks/month of moderate-to-severe intensity over a 3-month period or 6 migraine days during 4-week observation period • Normal findings on medical and laboratory assessments	• More than 18 headache days during the 4-week observation period • History of non-responsiveness to more than 2 types of preventative migraine treatment • Had a medical condition that would expose undue risk or interfere with the assessment of efficacy or safety • Drug or alcohol abuse treatment in the past 12 months • History of drug allergy or another allergy that made them unsuitable • Had an ECG or laboratory test findings that raised safety or tolerability concerns

This study was conducted using a tablet formulation of rimegepant 75 mg; the formulation of VYDURA used within the UK is oral lyophilisate 75 mg.[2,31] Permitted rescue medications during the 12-week double-blind treatment phase included triptans, NSAIDs, paracetamol up to 1,000 mg/day for a maximum of 2 consecutive days (including a fixed combination containing paracetamol 250 mg, aspirin 250 mg and caffeine 65 mg), baclofen, antiemetics and muscle relaxants. Rimegepant was not permitted as a rescue medication.[2,31]

Hierarchical Gate Keeping

To control the type I statistical error rate at 0.05, a hierarchical gate-

keeping procedure was applied, with a prespecified sequence of comparisons from the co-primary endpoint through to the secondary endpoints in the order listed in the protocol.[31]

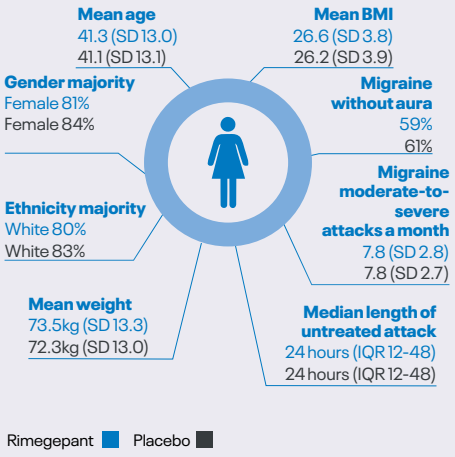
Primary and secondary endpoints

The primary endpoint was change from 4-week observation period (baseline) in mean MMD in weeks 9 to 12 in the double-blind phase.[2,31]

Secondary efficacy endpoints are numbered in the table below from 1 to 6 in order of hierarchal testing. The secondary endpoints related to safety and tolerability were the frequency of unique participants with: AEs; serious AEs; AEs leading to discontinuation; clinically significant laboratory test abnormalities; increases in aspartate aminotransferase or alanine aminotransferase greater than 3 times the upper limit of normal (ULN) concurrently with bilirubin elevations greater than 2 times the ULN; and hepatic-related AEs and hepatic-related AEs leading to discontinuation of treatment.[31]

Secondary efficacy endpoints[31]
Related to migraine and rescue medication[31]
Secondary endpoint 1/6. At least 50% reduction from 4-week observation period (baseline) in mean number of moderate-to-severe MMD during weeks 9 to 12
Secondary endpoint 2/6. Change from baseline in MMD during weeks 1 to 12
Secondary endpoint 3/6. Mean number of rescue medication days per month during weeks 9 to 12
Secondary endpoint 4/6. Change from baseline in MMD during weeks 1 to 4
Related to disability[31]
Secondary endpoint 5/6. Change from baseline in Migraine-Specific Quality-of-Life Questionnaire (MSQ) role function at Week 12
Secondary endpoint 6/6. Change from baseline in Migraine Disability Assessment (MIDAS) total score at Week 12

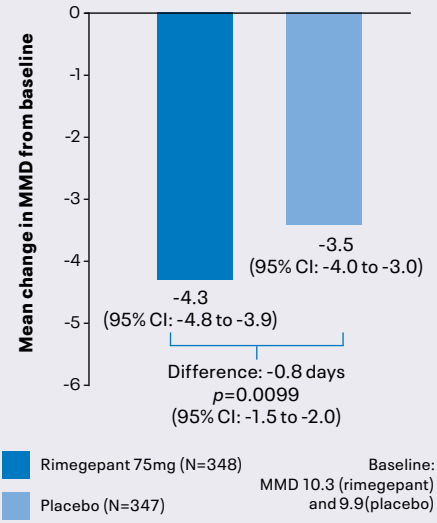
Figure 10. Baseline characteristics (N=741)[31]



Rimegepant for the prevention of episodic migraine (Study 305)

Figure 11. Rimegepant can prevent episodic migraines by reducing MMDs from baseline during weeks 9-12 vs placebo[31]

Primary endpoint: statistically significant reduction in mean MMD from baseline during weeks 9-12 with rimegepant compared to placebo[31]



Mean change in MMD from baseline during weeks 9 to 12 in patients receiving rimegepant compared to placebo. Adapted from Croop et al. 2021[31]

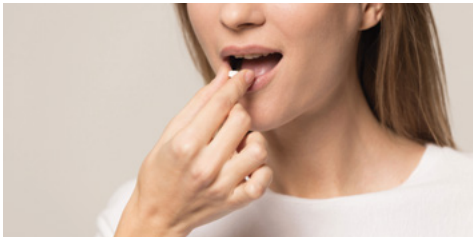
The primary efficacy endpoint was analysed using a generalised linear mixed effects model with treatment group, preventative migraine medication use at randomisation, study month, and month-by-treatment group interaction as fixed effects and participant as random effect.[31]

The secondary efficacy endpoint analysis showed a significant change with rimegepant vs. placebo in patients with ≥50% reduction from baseline in the mean number of moderate or severe migraine monthly days (MMD) during weeks 9-12 and change from baseline in MMD across weeks 1 to 12.[31]

Secondary endpoint analysis for rimegepant (N=348) vs. placebo (N=347)[31]

Secondary endpoint 1/6. ≥50% reduction in mean MMD during weeks 9 to 12 (8% difference; *p*=0.044; 95% CI: 0 to 15)

Secondary endpoint 2/6. Reduction in mean MMD from week 1 to week 12 (-0.8 days difference; *p*=0.0017; 95% CI: -1.3 to -0.3)



Not a real patient, for illustrative purposes only

Scan the QR code for additional data on secondary endpoints.

Not a real patient, for illustrative purposes only

	Rimegepant 75 mg (n=370)[31]	Placebo (n=371)[31]
Participants with AEs	133 (36%)	133 (36%)
AEs reported in at least 2% of participants treated with rimegepant[31]		
Nasopharyngitis	13 (4%)	9 (2%)
Nausea	10 (3%)	3 (1%)
Urinary tract infection	9 (2%)	8 (2%)
Upper respiratory tract infection	8 (2%)	10 (3%)
Participants with mild AEs	92 (25%)	91 (25%)
Participants with moderate AEs	64 (17%)	62 (17%)
AEs related to treatment	40 (11%)	32 (9%)
Serious AEs	3 (1%)	4 (1%)
Serious AEs related to treatment	0	1 (<1%)
AEs leading to discontinuation	7 (2%)	4 (1%)

Table 3: Adverse events reporting in Study 305[31]

4 rimegepant and 2 placebo participants had concentrations of aspartate aminotransferase (AST) and alanine transaminase (ALT) >3x the ULN.[31]

1 (<1%) participant in the rimegepant group had bilirubin levels >2x the ULN and was diagnosed with a hereditary liver disorder (Gilbert syndrome) after genotyping.[31]

Posology, contraindications, and special warnings

Please refer to the summary of product characteristics (SPC) for full information.

For acute treatment of migraine: the recommended dose is 75 mg VYDURA, as needed, once daily.[2]

For preventative treatment: the recommended dose is 75 mg VYDURA every other day.[2]

No more than one oral lysophilisate should be taken in a 24-hour period.[2]

Scan the QR code to view the prescribing information

Patients should be advised to use dry hands when opening the blister and refer to the package leaflet for complete instructions[2]

The maximum dose per day of VYDURA is 75 mg.[2]

Contraindications[2]

Hypersensitivity to the active substance or to any of the excipients (gelatine, mannitol (E421), mint flavour, sucralose).[2]

Special warnings and precautions for use

Hypersensitivity reactions, including dyspnoea and rash, have occurred in less than 1% of patients treated with rimegepant in clinical studies. Hypersensitivity reactions, including serious hypersensitivity, can occur days after administration. If a hypersensitivity reaction occurs, rimegepant should be discontinued and appropriate therapy should be initiated.

VYDURA is not recommended:

- in patients with severe hepatic impairment
- in patients with end-stage renal disease (CrCl <15 ml/min)
- for concomitant use with strong inhibitors of cytochrome P450 3A4 (CYP3A4)
- for concomitant use with strong or moderate inducers of CYP3A4

Special populations

Elderly (aged 65 and over)[2]

There is limited experience with rimegepant in patients aged 65 years or older. No dose adjustment is required as the pharmacokinetics of rimegepant are not affected by age.

Renal impairment[2]

No dose adjustment is required in patients with mild, moderate, or severe renal impairment. Severe renal impairment resulted in a >2-fold increase in unbound area under the curve (AUC) but less than a 50% increase in total AUC (see section 5.2 of SPC). Caution should be exercised during frequent use in patients with severe renal impairment. Rimegepant has not been studied in patients with end-stage renal disease and in patients on dialysis. Use of rimegepant in patients with end-stage renal disease (CLcr <15 ml/min) should be avoided.

Hepatic impairment[2]

No dose adjustment is required in patients with mild (Child-Pugh A) or moderate

(Child-Pugh B) hepatic impairment. Plasma concentrations (unbound AUC) of rimegepant were significantly higher in subjects with severe (Child-Pugh C) hepatic impairment (see section 5.2 of SPC). The use of rimegepant in patients with severe hepatic impairment should be avoided.

Paediatric population[2]

The safety and efficacy of VYDURA in paediatric patients (< 18 years of age) have not been established. No data are available.

Medication overuse headache (MOH)[2]

Overuse of any type of medicinal product for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of medicinal products for acute headache.

Not a real patient, for illustrative purposes only

Interactions

Rimegepant is a substrate of CYP3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters.

CYP3A4 inhibitors[2]	• Inhibitors of CYP3A4 increase plasma concentrations of rimegepant • Concomitant administration of rimegepant with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ritonavir) is not recommended • Concomitant administration of rimegepant with itraconazole resulted in a significant increase in rimegepant exposure area under curve (AUC) by 4-fold and plasma peak concentration (C_{max}) 1.5-fold • Concomitant administration of rimegepant with medicinal products that moderately inhibit CYP3A4 (e.g., diltiazem, erythromycin, fluconazole) may increase exposure to rimegepant • Concomitant administration of rimegepant with fluconazole resulted in increased exposures of rimegepant (AUC by 1.8-fold) with no relevant effect on C_{max} • Another dose of rimegepant within 48 hours should be avoided when it is concomitantly administered with moderate inhibitors of CYP3A4 (e.g., fluconazole)
CYP3A4 inducers[2]	• Inducers of CYP3A4 decrease plasma concentrations of rimegepant • Concomitant administration of VYDURA with strong CYP3A4 inducers (e.g., phenobarbital, rifampicin, St John's wort (Hypericum perforatum) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, modafinil) is not recommended • The effect of CYP3A4 induction may last for up to 2 weeks after discontinuation of the strong or moderate CYP3A4 inducer • Concomitant administration of rimegepant with rifampicin resulted in a significant decrease (AUC reduced by 80% C_{max} and by 64%) in rimegepant exposure, which may lead to loss of efficacy
P-gp and BCRP only inhibitors[2]	• Inhibitors of P-gp and breast cancer resistance protein (BCRP) efflux transporters may increase plasma concentrations of rimegepant. Another dose of VYDURA within 48 hours should be avoided when it is concomitantly administered with strong inhibitors of P-gp (e.g., cyclosporine, verapamil, quinidine) • Concomitant administration of rimegepant with cyclosporine (a potent P-gp and BCRP inhibitor) or with quinidine (a selective P-gp inhibitor) resulted in a significant increase of similar magnitude in rimegepant exposure (AUC and C_{max} by > 50%, but less than 2-fold)

Fertility, pregnancy, and lactation

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Pregnancy[2]
There are limited data on the use of rimegepant in pregnant women. Animal studies demonstrate that rimegepant is not embryocidal, and no teratogenic potential has been observed at clinically relevant exposures. Adverse effects on embryo-foetal development (decreased foetal body weight and increased skeletal variations in rats) were only observed at exposure levels associated with maternal toxicity (approximately 200 times greater than clinical exposures) following administration of rimegepant during pregnancy. As a precautionary measure, it is preferable to avoid the use of VYDURA during pregnancy.

Breastfeeding[2]
In a single-centre study of 12 breastfeeding women treated with a single dose of rimegepant 75 mg, minimal concentrations of rimegepant were observed in breast milk. The relative percentage of a maternal dose estimated to reach the infant is less than 1%. There are no data on the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYDURA and any potential adverse reactions on the breastfed infant from rimegepant or from the underlying maternal condition.

Fertility[2]
Animal studies showed no clinically relevant impact on female and male fertility. Please see SPC for details.

Scan the QR code for more resources, including a patient headache diary
(This link takes you to a promotional website developed and funded by Pfizer Ltd.)

Guidance for the management of migraine

What self-care advice should I give to a person with migraine?[32]

- Keeping a headache diary can be helpful in identifying triggers and monitoring the effectiveness of treatment
- Avoidance of known triggers and lifestyle changes such as stress management, good sleep hygiene, adequate hydration, regular meals, exercise, and maintenance of a healthy weight can help
- MOH is common in people with migraine and can be avoided by restriction of acute medication to a maximum of 2 days per week
- Ensure that women who have migraine with aura are not using combined hormonal contraception, as this is contraindicated

NICE first-line treatment recommendations for acute migraine (Sept 2022)[32]

Depending on the severity of attacks, associated symptoms, contraindications, and comorbidities:[32]

- Offer simple analgesic such as ibuprofen (400mg, increased to 600mg if 400mg is ineffective), aspirin (900mg*), or paracetamol (1000mg)
- Offer a triptan, alone or in combination, with paracetamol or an NSAID. Oral sumatriptan is first choice (50-100mg)
- Consider offering an anti-emetic (such as metoclopramide 10mg or prochlorperazine 10mg) in addition to other acute medication even in the absence of nausea and vomiting

NICE and SMC now recommend VYDURA as an option for the acute treatment of migraine with or without aura in adults only if for previous migraine:[3,33]

- At least 2 triptans were tried and they did not provide adequate relief,[3,33] OR
- Triptans were contraindicated or not tolerated, and NSAIDs and paracetamol provide inadequate pain relief[3,33]

NICE do not specifically stated whether VYDURA should be prescribed in primary or secondary care for the treatment of acute migraine.[33]

When to consider preventive treatment for migraine

The aim of preventive treatment is to reduce the frequency, severity, and duration of migraine attacks, as well as to avoid MOH[32]

Consider preventive treatment if:[32]

- Migraine attacks are having a significant impact on quality of life; despite optimal acute treatment, they occur more than once a week on average or are prolonged and severe
- Acute treatments are contraindicated or ineffective
- Frequent acute drug use puts them at risk of MOH

NICE first-line treatment recommendations for prevention of migraine (Sept 2022)[32]

- Choice of preventative medication depends on contraindications, comorbidities, and risk of adverse events

Consider pharmacological therapies:[32]

- Such as, propranolol (80–160mg daily, in divided doses), topiramate* (50–100mg daily, in divided doses), or amitriptyline (25–75mg at night)

Discuss risks of Topiramate in women of childbearing potential, contraindicated in pregnancy, highly effective contraception is required prior to initiation[32]

Consider non-pharmacological therapies as an adjunct or alternative to pharmacological therapy depending on the specific clinical situation and the person's preference[32]

NICE and SMC now recommend VYDURA as an option for preventing episodic migraine in:[34,35]

- Adults with at least 4 and fewer than 15 migraine attacks/days[†] per month AND
- Only if at least 3 preventive treatments have not worked

VYDURA should be stopped after 12 weeks of treatment if the frequency of migraine does not reduce by at least 50%.[34] If VYDURA is considered to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all options, use the least expensive.[34] Administration costs, dosage, price per dose and commercial arrangements should be accounted for.[34] For use as a preventive treatment for episodic migraine, VYDURA may be likely prescribed by a specialist in secondary care; however, it could also be prescribed in primary care by GPs following Advice and Guidance from a specialist or within a shared care agreement.[34]

Other available fourth-line treatments on the NHS are the injectable monoclonal antibodies erenumab, fremanezumab and galcanezumab.[34]

[†]SMC guidance states fewer than 15 headache days per month; NICE guidance states fewer than 15 migraine attacks per month[34,35]

Not a real patient, for illustrative purposes only

What's next for Preeti?

Case study (not a real patient)

Preeti's migraine attacks are becoming more severe, with her current medication taking little effect. She is having to take more sick days each month, which is affecting her ability to do her job.
As Preeti has now failed 2 triptans, her GP explains that another class of medication that could be suitable is a CGRP receptor antagonist, such as VYDURA.[32,33]

Preeti agrees that she would like to try a new class of medications. Preeti is prescribed VYDURA for the acute treatment of migraine.[33] Her GP also booked her in for a 8-week follow-up appointment to reassess her migraine management.[32]

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Prescribing information

PRESCRIBING INFORMATION FOR GREAT BRITAIN AND NORTHERN IRELAND

▼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 of the SmPC for how to report adverse reactions.

VYDURA®▼(rimegepant)

Prescribing Information:

Please refer to the Summary of Product Characteristics (SmPC) before prescribing VYDURA 75 mg oral lyophilisate. **Presentation:** Oral lyophilisates containing 75 mg rimegepant. **Indications:** Acute treatment of migraine with or without aura in adults. Preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month. **Dosage:** For acute treatment of migraine, the recommended dose is 75 mg rimegepant, as needed, once daily. For prophylaxis of migraine, the recommended dose is 75 mg rimegepant every other day. The maximum dose per day is 75 mg rimegepant. Another dose of rimegepant should be avoided within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 or with strong inhibitors of P-gp (see SmPC section 4.5). VYDURA can be taken with or without meals. The oral lyophilisate should be placed on the tongue or under the tongue. It will disintegrate in the mouth and can be taken without liquid. Patients should be advised to use dry hands when opening the blister and referred to the package leaflet for complete instructions. No dose adjustment is required in patients aged 65 and over as the pharmacokinetics of rimegepant are not affected by age (see SmPC section 5.2). No dose adjustment is required in patients with mild, moderate, or severe renal impairment. Caution should be exercised during frequent use in patients with severe renal impairment. Use of rimegepant in patients with end-stage renal disease (CLcr < 15 ml/min) should be avoided. No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The use of rimegepant in patients with severe hepatic impairment should be avoided. The safety and efficacy of VYDURA in paediatric patients (< 18 years of age) have not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in SmPC section 6.1. **Warnings and Precautions:** Hypersensitivity reactions, including dyspnoea and rash, have occurred in less than 1% of patients treated with rimegepant in clinical studies (see SmPC section 4.8). Hypersensitivity reactions, including serious hypersensitivity, can occur days after administration. If a hypersensitivity reaction occurs, rimegepant should be discontinued and appropriate therapy should be initiated. VYDURA is not recommended in patients with severe hepatic impairment (see SmPC section 4.2), in patients with end-stage renal disease (CLcr < 15 ml/min) (see SmPC section 4.2), for concomitant use with strong inhibitors of CYP3A4 (see SmPC section 4.5) or for concomitant use with strong or moderate inducers of CYP3A4 (see SmPC section 4.5). If overuse is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of medicinal products for acute headache.

Drug Interactions: Rimegepant is a substrate of CYP3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters (see SmPC section 5.2). Concomitant administration of rimegepant with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ritonavir) is not recommended (see SmPC section 4.4). Concomitant administration of rimegepant with itraconazole resulted in a significant increase in rimegepant exposure (AUC by 4-fold and Cmax 1.5-fold). Concomitant administration of rimegepant with medicinal products that moderately inhibit CYP3A4 (e.g., diltiazem, erythromycin, fluconazole) may increase exposure to rimegepant. Concomitant administration of rimegepant with fluconazole resulted in increased exposures of rimegepant (AUC by 1.8-fold) with no relevant effect on Cmax. Another dose of rimegepant within 48 hours should be avoided when it is concomitantly administered with moderate inhibitors of CYP3A4 (e.g., fluconazole) (see SmPC section 4.2). Concomitant administration of VYDURA with strong CYP3A4 inducers (e.g., phenobarbital, rifampicin, St John's wort (Hypericum perforatum)) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, modafinil) is not recommended (see SmPC section 4.4). The effect of CYP3A4 induction may last for up to 2 weeks after discontinuation of the strong or moderate CYP3A4 inducer. Concomitant administration of rimegepant with rifampicin resulted in a significant decrease (AUC reduced by 80% and Cmax by 64%) in rimegepant exposure, which may lead to loss of efficacy. Inhibitors of P-gp and BCRP efflux transporters may increase plasma concentrations of rimegepant. Another dose of VYDURA within 48 hours should be avoided when it is concomitantly administered with strong inhibitors of P-gp (e.g., cyclosporine, verapamil, quinidine) (see SmPC section 4.2 and 4.5). Concomitant administration of rimegepant with cyclosporine (a potent P-gp and BCRP inhibitor) or with quinidine (a selective P-gp inhibitor) resulted in a significant increase of similar magnitude in rimegepant exposure (AUC and Cmax by > 50%, but less than two-fold). **Pregnancy & Lactation:** There are limited data from the use of rimegepant in pregnant women. Animal studies demonstrate that rimegepant is not embryocidal, and no teratogenic potential has been observed at clinically relevant exposures. As a precautionary measure, it is preferable to avoid the use of VYDURA during pregnancy. The relative percentage of a maternal dose estimated to reach the infant is less than 1%. There are no data on the effects on milk production. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for VYDURA and any potential adverse reactions on the breastfed infant from rimegepant or from the underlying maternal condition. Driving and **Operating Machinery:** VYDURA has no or negligible influence on the ability to drive and use machines. **Side Effects:** The most common adverse reaction was nausea for acute treatment (1.2%) and for migraine prophylaxis (1.4%). Most of the reactions were mild or moderate in severity. Hypersensitivity, including dyspnoea and severe rash were uncommon side effects observed in the acute treatment and occurred in less than 1% of patients treated. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred. **Legal Category:** POM. **Marketing Authorisation Holder Northern Ireland (NI):** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium. **Marketing Authorisation Numbers for NI:** EU/1/22/1645/001, EU/1/22/1645/002 **Marketing Authorisation Holder Great Britain (GB):** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom Marketing Authorisation Number for GB: PLGB 00057/1717 **Local Representative:** Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. Package quantities, Basic NHS Price: VYDURA 75 mg, 2 x 1 oral lyophilisates, £25.80; 8 x 1 oral lyophilisates, £103.20.

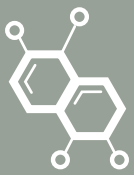
PP-NNT-GBR-0700 July 2023

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Pfizer Medical Information on 01304 616161.

Material job code: October 2023 | PP-NNT-GBR-1007

Migraine is the second leading cause of years lived with disability[5]

In the UK alone, it is estimated that 3 million workdays are lost every year to migraine-related absenteeism[5]



VYDURA selectively binds with high affinity to the CGRP receptor, thereby antagonising its function.[2] The relationship between pharmacodynamic activity and the mechanism(s) by which VYDURA exerts its clinical effects is unknown[2]

VYDURA is indicated for the acute treatment of migraine with or without aura in adults or the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month[2]

For more information visit: https://www.pfizerpro.co.uk/medicine/vydura
This links to a promotional website developed and funded by Pfizer Ltd.

October 2023 | PP-NNT-GBR-1007