swissmedic

Date: 12 December 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vydura

International non-proprietary name: rimegepant
Pharmaceutical form: oral lyophilisate
Dosage strength(s): 75 mg
Route(s) of administration: oral
Marketing authorisation holder: Pfizer AG
Marketing authorisation no.: 69035
Decision and decision date: approved on 18 October 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

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

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for rimegepant in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Vydura is indicated for the
- 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.

2.2.2 Approved indication

Vydura is indicated for the
- Acute treatment of migraine attacks with or without aura in adults.
- Prophylactic treatment of episodic migraine in adults, if indicated.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Acute treatment of migraine: the recommended dose is 75 mg rimegepant, as needed, once a day.
Prevention of migraine: the recommended dose is 75 mg of rimegepant every other day.
The maximum daily dose of rimegepant is 75 mg

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	11 July 2022
Formal objection	8 August 2022
List of Questions (LoQ)	22 November 2022
Response to LoQ	15 February 2023
Preliminary decision	15 May 2023
Response to preliminary decision	13 July 2023
Labelling corrections	26 September 2023
Response to labelling corrections	3 October 2023
Final decision	18 October 2023
Decision	approval

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3 Medical context

Migraine is a common neurological disorder that affects around 5% of the adult population (1-year prevalence: 8% in men, 20% in women) in western countries. It is characterised by episodic, often disabling headache, associated with sensory (aura) and autonomic symptoms (nausea, vomiting), phonophobia and photophobia, and cognitive symptoms. Migraine attacks typically last from 4 to 72 hours if untreated or unsuccessfully treated.
Episodic migraine (EM) is defined as <15 headache days per month, although in clinical prophylactic trials a lower threshold of a minimum of 4 headache days is often chosen to reflect typical patients in need of a prophylactic treatment. Chronic migraine (CM) is defined as 15 or more headache days per month. At least 8 of these 15 or more headache days have to be typical migraine days.
There are established and approved substances for the acute treatment of migraine symptoms (such as triptans), and substances for the prevention of migraine attacks (such as beta blockers or topiramate). Not all patients respond to the respective treatments, and often, several substances have to be tested sequentially to find a suitable treatment option. There is still a clear need for additional options for acute treatment and prophylaxis of migraine attacks.

Growing evidence indicates that calcitonin gene-related peptides (CGRPs) play a key role in peripheral sensitisation and associated enhanced pain, and that these peptides are involved in migraine pathophysiology. Blocking the calcitonin gene-related peptide (CGRP) or the CGRP receptor has emerged as a possible mechanism for the prevention of migraine attacks, as well as for the treatment of acute migraine attacks. Amongst others, decreasing blood flow in cerebral vessels and inhibition of pain transmission in the trigeminal ganglion are discussed as possible mechanisms for CGRG-blocking agents.
While consistent efficacy and a good safety profile have been observed for the antibodies targeting the CGRP pathway, they have to be injected subcutaneously or intravenously, and have a long half-life, which makes them less flexible in case of treatment regimen changes. Oral CGRP antagonists with a shorter half-life (rimegepant, ubrogepant, atogepant) have been approved in the US and recently in the EU (rimegepant, atogepant) for the acute treatment of migraine attacks (rimegepant, ubrogepant) or for the prevention of migraine attacks (rimegepant, atogepant). Migraine therapy with a short-acting oral agent for treatment of acute migraine attacks and for the prevention of future attacks could simplify the medication regimen, offer more flexibility when adverse effects occur, avoid polypharmacy, and reduce the risk of drug-drug interactions.

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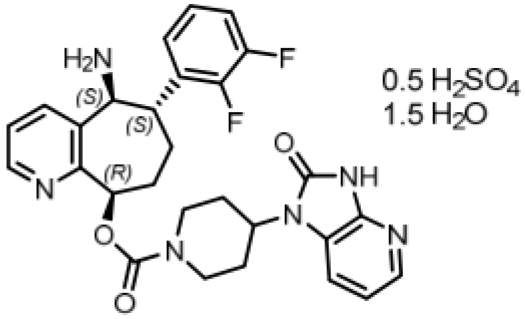
4 Quality aspects

4.1 Drug substance

INN:
Rimegepant (used as rimegepant hemisulfate sesquihydrate)
Chemical name:
(5S,6S,9R)-5-Amino-6-(2,3-difluorophenyl)-6,7,8,9 tetrahydro-*5H*-cyclohepta[*b*]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidine-1-carboxylate hemisulfate sesquihydrate
Molecular formula:
$C_{28}H_{28}F_2N_6O_3 \cdot 0.5H_2SO_4 \cdot 1.5H_2O$
Molecular mass:
610.63 (sesquihydrate) / 534.57 (free base)
Molecular structure:



Physico-chemical properties:
White to off-white, slightly hygroscopic powder; freely soluble in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF); slightly soluble in methanol and water; very slightly soluble in ethanol, acetone, n-butanol, tetrahydrofuran, and acetonitrile; and practically insoluble in ethyl acetate. Its solubility decreases with increasing pH. Rimegepant exhibits stereoisomerism due to the presence of three chiral centres. The substance shows polymorphism but a defined form is produced.

Synthesis:
The chemical synthesis consists of several steps, involving two key intermediates.

Specification:
In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
Appropriate stability data have been presented. Based on the results, satisfactory re-test periods have been established when stored in sealed packaging as proposed in the application.

4.2 Drug product

Description and composition:
The final product is a white to off-white circular oral lyophilisate containing 75mg of rimegepant free base (used as hemisulfate salt). The oral lyophilisate is designed to rapidly disintegrate in the mouth and does not require a reconstitution diluent. The lyophilisates are packed in blister strips.

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Pharmaceutical development:
The objective of the development was to provide a stable, oral lyophilisate of consistent quality, containing 75mg of rimegepant free base and suitable excipients. The oral lyophilisate is easy to administer, rapidly disintegrating in the mouth before swallowing.

Manufacture:
The manufacturing process consists of several steps, including freeze-drying and heat sealing/packaging.

Specification:
For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include relevant physico-chemical characteristics, identification of the drug substance, as well as assay and purity tests. The corresponding test procedures have been validated.

Container closure system:
The oral lyophilisates are packed into opaque blisters (containing aluminium, amongst other components).

Stability:
Appropriate stability data have been generated for the product packed in blisters, according to the relevant international guidelines. The storage recommendation is “Do not store above 30 °C”, and to keep the product in its original container in order to protect it from moisture.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

Regarding the marketing authorisation application for Vydura (rimegepant), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the European Medicines Agency (EMA) assessment report (EMA/CHMP/105848/2022) that was provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Vydura in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There are no safety concerns regarding impurities and excipients.

Based on the available data it is not possible to draw a conclusion on the potential risk of rimegepant to the environment. A phase II ERA for the active substance has been requested (post-approval requirement).

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6 Clinical aspects

6.1 Clinical pharmacology and clinical aspects

The evaluation of the clinical pharmacology data and the clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA and the FDA. The available EMA assessment report (EMA/CHMP/172260/2022) and the FDA report and respective product information from the EMA and FDA were used as a basis for the clinical pharmacology and the clinical evaluation. For further details concerning clinical pharmacology, efficacy and safety, please consider chapter 8 of this report.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved information for healthcare professionals

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

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

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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Information for healthcare professionals

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Vydura

Composition

Active substances

Rimegepantum ut rimegepanti hemisulfas sesquihydricus.

Excipients

Gelatinum, mannitolum (E 421), Aromatica (mentha) cum alcohol benzylicus, sucralosum.

Pharmaceutical form and active substance quantity per unit

Oral lyophylisate.

One oral lyophylisate contains 75 mg Rimegepant (as Rimegepanthemisulfat-Sesquihydrat).

The oral lyophylisate is white to off-white, circular, diameter 14 mm and debossed with the symbol .

Indications/Uses

Vydura is indicated for the

- Acute treatment of migraine attacks with or without aura in adults.
- Prophylactic treatment of episodic migraine in adults, if indicated.

Dosage/Administration

The indication for the therapy should be issued by a physician with experience in the area of migraine treatment and should be accompanied throughout the treatment.

Information for healthcare professionals

Acute treatment of migraine

The recommended dose is 75 mg rimegepant, as needed, once daily.

Prevention of migraine

The recommended dose is 75 mg rimegepant every other day.

The maximum dose per day is 75 mg rimegepant.

Dose adjustment following undesirable effects/interactions

Another dose of rimegepant should be avoided within 48 h when it is concomitantly administered with moderate inhibitors of CYP3A4 or with strong inhibitors of P-gp (see «Interactions»).

Special dosage instructions

Patients with hepatic disorders

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 «Pharmacokinetics»). The use of rimegepant in patients with severe hepatic impairment should be avoided.

Patients with renal disorders

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 AUC but less than a 50% increase in total AUC (see «Pharmacokinetics»). 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.

Elderly patients

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 (see «Pharmacokinetics»).

Information for healthcare professionals

Children and adolescents

The safety and efficacy in children and adolescents under 18 years have not been demonstrated. No data are available.

Mode of administration

Vydura is for oral use.

Vydura can be taken with or without meals.

Vydura 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 should be referred to the package leaflet for complete instructions.

Contraindications

Hypersensitivity to the active substance or to any of the excipients of Vydura.

Warnings and precautions

Hypersensitivity reactions, including dyspnoea and rash, have occurred in less than 1% of patients treated with rimegepant in clinical studies (see «Undesirable effects»). 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 «Dosage/Administration»).
- in patients with end-stage renal disease (CLcr <15 ml/min) (see «Dosage/Administration»).
- for concomitant use with strong inhibitors of CYP3A4 (see «Interactions»).
- for concomitant use with strong or moderate inducers of CYP3A4 (see «Interactions»).

Patients not included in the clinical phase 3 trials:

Patients with uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia were excluded from the clinical phase 3 trials. In particular, subjects with myocardial infarction (MI), acute coronary syndrome (ACS),

percutaneous coronary intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during 6 months (24 weeks) prior to screening were excluded from participation.Rimegepant/Vydura should be used with caution in these patients.

Medication Overuse Headache (MOH)

Overuse of medicinal products for headaches can make them worse. Although there is no evidence that use of rimegepant up to once daily can lead to MOH, 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. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued.

Interactions

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

Pharmacokinetic interactions

Effect of other agents on the pharmacokinetics of rimegepant

CYP3A4 inhibitors

Inhibitors of CYP3A4 increase plasma concentrations of rimegepant. Concomitant administration of rimegepant with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ritonavir) is not recommended (see «Warnings and precautions»). Concomitant administration of rimegepant with itraconazole resulted in a significant increase in rimegepant exposure (AUC by 4-fold and 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 h should be avoided when it is concomitantly administered with moderate inhibitors of CYP3A4 (e.g., fluconazole) (see «Dosage/Administration»).

Information for healthcare professionals

CYP3A4 inducers

Inducers of CYP3A4 decrease plasma concentrations of rimegepant. Concomitant administration of rimegepant 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 «Warnings and precautions»). 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 C_{max} by 64%) in rimegepant exposure, which may lead to loss of efficacy.

P-gp and BCRP only inhibitors

Inhibitors of P-gp and BCRP efflux transporters may increase plasma concentrations of rimegepant. Another dose of rimegepant within 48 h 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 two-fold). Therefore, concomitant administration of rimegepant with BCRP inhibitors is not expected to have a clinically significant impact on rimegepant exposures.

Other medicinal products

No significant pharmacokinetic interactions were observed when Vydura was concomitantly administered with oral contraceptives (norelgestromin, ethinyl estradiol), midazolam (a sensitive CYP3A4 substrate), metformin (a MATE1 substrate), or sumatriptan.

No clinically relevant differences in resting blood pressure were observed when rimegepant was concomitantly administered with sumatriptan (12 mg subcutaneous, given as two 6 mg doses separated by one hour) compared with sumatriptan alone to healthy volunteers.

In vitro Assessments

Metabolism

Based on *in vitro* studies, rimegepant is not an inhibitor of CYP1A2, 2B6, 2C9, 2C19, 2D6, or UGT1A1 at clinically relevant concentrations. However, rimegepant is a weak inhibitor of CYP3A4 with time-dependent inhibition. Rimegepant is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Information for healthcare professionals

Transporters

In vitro, rimegepant is a substrate of P-gp and BCRP efflux transporters. Inhibitors of P-gp and BCRP efflux transporters may increase plasma concentrations of rimegepant (see «Interactions»).

Rimegepant is not a substrate of OATP1B1 or OATP1B3. Considering its low renal clearance, rimegepant was not evaluated as a substrate of the OAT1, OAT3, OCT2, MATE1, or MATE2-K.

Rimegepant is not an inhibitor of P-gp, BCRP, OAT1, or MATE2-K at clinically relevant concentrations. It is a weak inhibitor of OATP1B1 and OAT3.

Rimegepant is an inhibitor of OATP1B3, OCT2, and MATE1. Concomitant administration of rimegepant with metformin, a MATE1 transporter substrate, resulted in no clinically significant impact on either metformin pharmacokinetics or on glucose utilization. No clinical drug interactions are expected for rimegepant with OATP1B3 or OCT2, at clinically relevant concentrations.

Pregnancy, lactation

Pregnancy

There are limited data from the use of rimegepant in pregnant women. Animal studies demonstrated that rimegepant is not embryocidal, and no teratogenic potential has been observed at clinically relevant exposures (see «Preclinical data»). As a precautionary measure, it is preferable to avoid the use of Vydura during pregnancy.

Lactation

In a single center study of 12 breast-feeding 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 breast-feeding should be considered along with the mother’s clinical need for rimegepant and any potential adverse reactions on the breastfed infant from rimegepant or from the underlying maternal condition.

Fertility

The effects of rimegepant on human fertility were not studied.

Animal studies showed no clinically relevant impact on female and male fertility (see «Preclinical data»)

Information for healthcare professionals

Effects on ability to drive and use machines

No corresponding studies have been performed. Vydura has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Long-term safety

Long-term safety of rimegepant was assessed in two one year, open-label extensions; 1662 patients received rimegepant for at least 6 months and 740 patients received rimegepant for 12 months for acute or preventive treatment.

Summary of the safety profile

The most common adverse reaction was nausea for acute treatment (1.2%) and for migraine prevention (1.4%). Most of the reactions were mild or moderate in severity. Hypersensitivity, including dyspnoea and severe rash, occurred in less than 1% of patients treated.

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows: «common» (≥1/100, <1/10), «uncommon» (≥1/1’000, <1/100).

Acute treatment

Immune system disorders

Uncommon: Hypersensitivity, including dyspnoea and severe rash.

Gastrointestinal disorders

Common: Nausea.

Prevention

Gastrointestinal disorders

Common: Nausea.

Description of specific adverse reactions and additional information

Hypersensitivity reactions

Hypersensitivity, including dyspnoea and severe rash, occurred in less than 1% of patients treated in clinical studies. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred.

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

Overdose

There is limited clinical experience with rimegepant overdose. No overdose symptoms have been reported. Treatment of an overdose of rimegepant should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. No specific antidote for the treatment of rimegepant overdose is available. Rimegepant is unlikely to be significantly removed by dialysis because of high serum protein binding.

Properties/Effects

ATC code

N02CD06.

Mechanism of action

Rimegepant selectively binds with high affinity to the human calcitonin gene-related peptide (CGRP) receptor and antagonizes CGRP receptor function.

Pharmacodynamics

The relationship between pharmacodynamic activity and the mechanism(s) by which rimegepant exerts its clinical effects is unknown.

Cardiac Electrophysiology

Information for healthcare professionals

At a single dose 4 times the recommended dose, rimegepant does not prolong the QT interval to any clinically relevant extent.

Clinical efficacy

Acute treatment

The efficacy of rimegepant for the acute treatment of migraine with and without aura in adults was studied in three randomized, double-blind, placebo-controlled trials (Studies 1-3). Patients were instructed to treat a migraine of moderate to severe headache pain intensity. Rescue medicinal products (i.e., NSAIDs, paracetamol, and/or an antiemetic) was allowed 2 h after the initial treatment. Other forms of rescue medicinal products such as triptans were not allowed within 48 h of initial treatment. Approximately 14% of patients were taking preventive medicinal products for migraine at baseline. None of the patients in Study 1 were on concomitant preventive medicinal products that act on the calcitonin gene-related peptide pathway.

The primary efficacy analyses were conducted in patients who treated a migraine with moderate to severe pain. Pain freedom was defined as a reduction of moderate or severe headache pain to no headache pain, and most bothersome symptom (MBS) freedom was defined as the absence of the self-identified MBS (i.e., photophobia, phonophobia, or nausea). Among patients who selected an MBS, the most commonly selected symptom was photophobia (54%), followed by nausea (28%), and phonophobia (15%).

In Study 1, the percentage of patients achieving headache pain freedom and MBS freedom at 2 h after a single dose was statistically significantly greater in patients who received rimegepant compared to those who received placebo (Table 1). In addition, statistically significant effects of rimegepant compared to placebo were demonstrated for the additional efficacy endpoints of pain relief at 2 h, sustained pain freedom from 2 to 48 h, use of rescue medication within 24 h, and ability to function normally at 2 h after dosing. Pain relief was defined as a reduction in migraine pain from moderate or severe severity to mild or none. Pivotal single attack, double-blind, placebo-controlled studies 2 & 3 were conducted in patients with migraine who received one 75 mg rimegepant bioequivalent dosage form.

Information for healthcare professionals

Table 1: Migraine Efficacy Endpoints for Acute Treatment Studies.

	Study 1		Study 2		Study 3	
	Rimegepant 75 mg	**Placebo**	**Rimegepant 75 mg**	**Placebo**	**Rimegepant 75 mg**	**Placebo**
Pain free at 2 h						
n/N*	142/669	74/682	105/537	64/535	104/543	77/541
% Responders	21.2	10.9	19.6	12.0	19.2	14.2
Difference compared to placebo (%)	10.3		7.6		4.9	
p-value		<0.0001[a]		0.0006[a]		0.0298[a]
MBS free at 2 h						
n/N*	235/669	183/682	202/537	135/535	199/543	150/541
% Responders	35.1	26.8	37.6	25.2	36.6	27.7
Difference compared to placebo (%)	8.3		12.4		8.9	
p-value		0.0009[a]		<0.0001[a]		0.0016[a]
Pain relief at 2 h						
n/N*	397/669	295/682	312/537	229/535	304/543	247/541
% Responders	59.3	43.3	58.1	42.8	56.0	45.7
Difference compared to placebo (%)	16.1		15.3		10.3	
p-value		<0.0001[a]		<0.0001[a]		0.0006[a]
Sustained pain freedom 2 to 48 h						
n/N*	90/669	37/682	53/537	32/535	63/543	39/541
% Responders	13.5	5.4	9.9	6.0	11.6	7.2
Difference compared to placebo (%)	8.0		3.9		4.4	
p-value		<0.0001[a]		NS		NS

*n=number of responders/N=number of patients in that treatment group

[a] Significant p-value in hierarchical testing

MBS: most bothersome symptom

NS: not significant in hierachical testing

Figure 1 presents the percentage of patients achieving migraine pain freedom within 2 h following treatment in Study 1.

Figure 1: Percentage of patients achieving pain freedom within 2 h in Study 1.

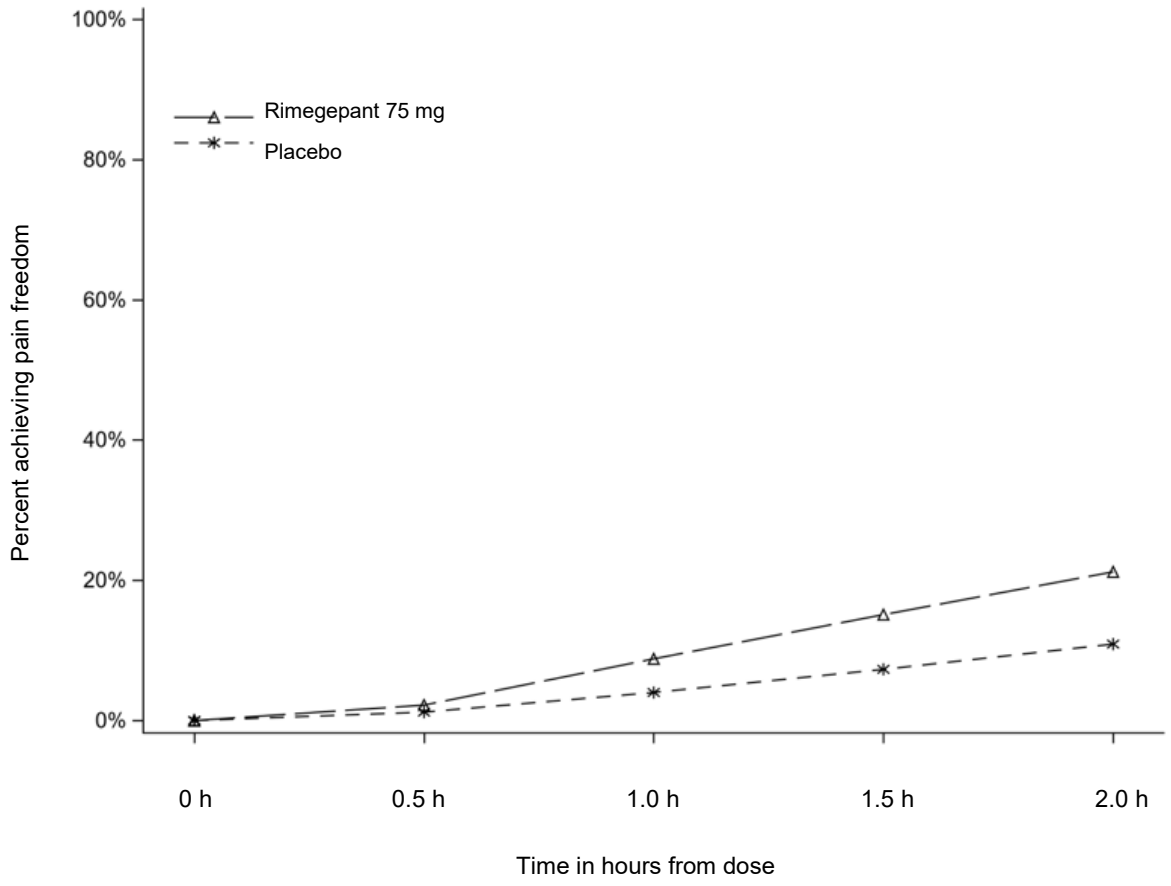
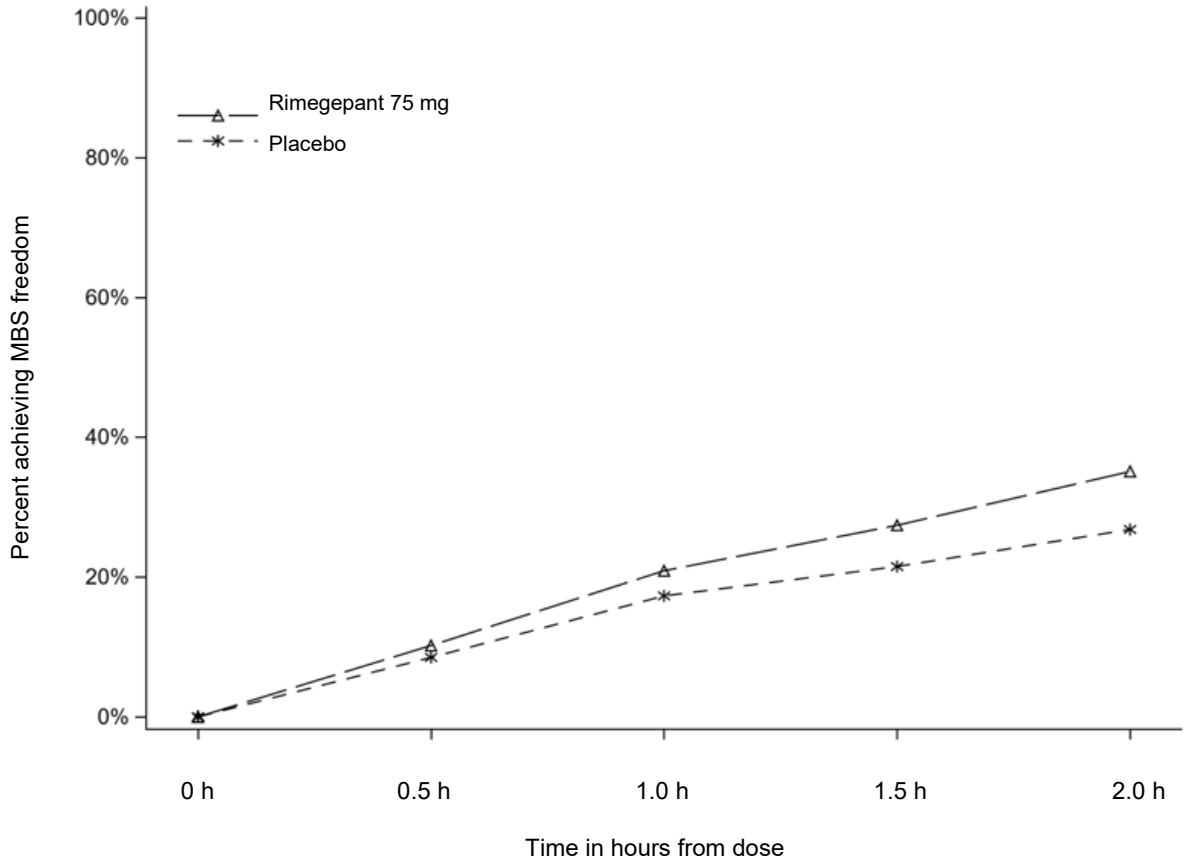


Figure 2 presents the percentage of patients achieving MBS freedom within 2 h in Study 1.

Figure 2: Percentage of patients achieving MBS freedom within 2 h in Study 1.



The incidence of photophobia and phonophobia was reduced at 2 h following administration of rimegepant 75 mg as compared to placebo in all 3 studies.

Prevention

The efficacy of rimegepant was evaluated as a preventive treatment of migraine in a randomized, double-blind, placebo-controlled study (Study 4).

Study 4 included male and female adults with at least a 1-year history of migraine (with or without aura). Patients had a history of 4 to 18 migraine attacks of moderate to severe pain intensity per 4-week period within the 12 weeks prior to the screening visit. Patients experienced an average of 10.9 headache days during the 28-day observational period, which included an average of 10.2 migraine days, prior to randomization into the study. The study randomized patients to receive rimgepant 75 mg (N=373) or placebo (N=374) for up to 12 weeks. Patients were instructed to take randomized treatment once every other day (EOD) for the 12-week treatment period. Patients were allowed to use other acute treatments for migraine (e.g., triptans, NSAIDs, paracetamol, antiemetics) as needed. Approximately 22% of patients were taking preventive medicinal products for migraine at

baseline. Patients were allowed to continue in an open-label extension study for an additional 12 months.

The primary efficacy endpoint for Study 4 was the change from baseline in the mean number of monthly migraine days (MMDs) during Weeks 9 through 12 of the double-blind treatment phase. Secondary endpoints included the achievement of a ≥50% reduction from baseline in monthly moderate or severe migraine days.

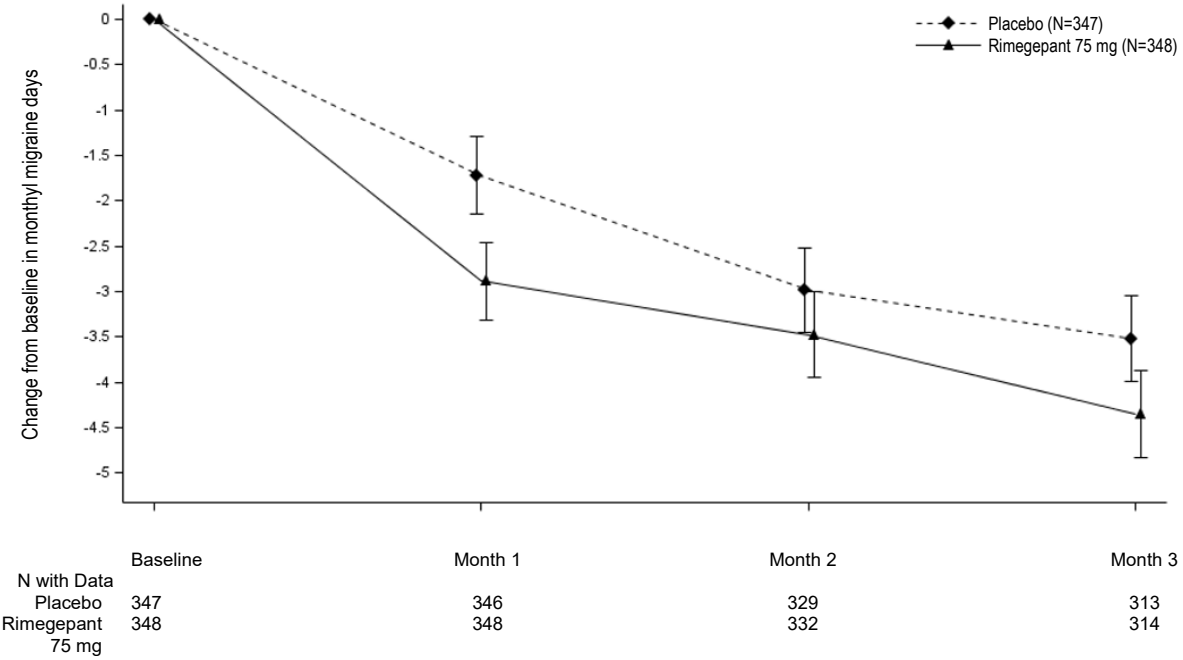
Rimegepant 75 mg dosed EOD demonstrated statistically significant improvements for key efficacy endpoints compared to placebo, as summarized in Table 3 and shown graphically in Figure 3.

Table 3: Key efficacy endpoints for Study 4.

	Rimegepant 75 mg EOD	**Placebo EOD**
Monthly Migraine Days (MMD) Weeks 9 through 12	**N=348**	**N=347**
Change from baseline	-4.3	-3.5
Change compared to placebo	-0.8	
p-value	0.010[a]	
≥50% Reduction in Moderate or Severe MMDs Weeks 9 through 12	**N=348**	**N=347**
% Responders	49.1	41.5
Difference compared to placebo	7.6	
p-value	0.044[a]	

[a] Significant p-value in hierarchical testing

Figure 3: Change from baseline in monthly migraine days in Study 4.



	Baseline	Month 1	Month 2	Month 3
N with Data				
Placebo	347	346	329	313
Rimegepant 75 mg	348	348	332	314

Long-term data

Patients participating in Study 4 were allowed to continue in an open-label extension study for an additional 12 months. Efficacy was sustained for up to 1 year in an open-label study extension in which patients received rimegepant 75 mg every other day plus as needed on non-scheduled dosing days. A portion composed of 203 patients assigned to rimegepant completed the overall 16-month treatment period. In these patients, the overall mean reduction from baseline in the number of MMDs averaged over the 16-month treatment period was 6.2 days.

Pharmacokinetics

Absorption

Following oral administration, rimegepant is absorbed with the maximum concentration at 1.5 h. Following a supratherapeutic dose of 300 mg, the absolute oral bioavailability of rimegepant was approximately 64%.

Effects of food

Following administration of rimegepant under fed conditions with a high-fat or low-fat meal, T_{max} was delayed by 1 to 1.5 h. A high-fat meal reduced C_{max} by 42 to 53% and AUC by 32 to 38%. A low-fat

meal reduced C_{max} by 36% and AUC by 28%. Rimegepant was administered without regard to food in clinical safety and efficacy studies.

Distribution

The steady state volume of distribution of rimegepant is 120 l. Plasma protein binding of rimegepant is approximately 96%.

Metabolism

Rimegepant is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9. Rimegepant is primarily eliminated in unchanged form (~77% of the dose) with no major metabolites (i.e., >10%) detected in plasma.

Elimination

The elimination half-life of rimegepant is approximately 11 h in healthy subjects. Following oral administration of [^{14}C]-rimegepant to healthy male subjects, 78% of the total radioactivity was recovered in feces and 24% in urine. Unchanged rimegepant is the major single component in excreted feces (42%) and urine (51%).

Linearity/non-linearity

Rimegepant exhibits greater than dose proportional increases in exposure following single oral administration, which appears to be related to a dose-dependant increase in bioavailability.

Kinetics in specific patient groups

No clinically significant differences in the pharmacokinetics of rimegepant were observed based on age, sex, ethnicity, body weight, migraine status, or CYP2C9 genotype.

Hepatic impairment

In a dedicated clinical study comparing the pharmacokinetics of rimegepant in subjects with mild, moderate, and severe hepatic impairment to that with normal subjects (healthy matched control), the exposure of rimegepant (unbound AUC) following a single 75 mg dose was 3.89-fold higher in subjects with severe impairment (Child-Pugh class C). There were no clinically meaningful differences

in the exposure of rimegepant in subjects with mild (Child-Pugh class A) and moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function.

Renal impairment

In a dedicated clinical study comparing the pharmacokinetics of rimegepant in subjects with mild (estimated creatinine clearance [CLcr] 60-89 ml/min), moderate (CLcr 30-59 ml/min), and severe (CLcr 15-29 ml/min) renal impairment to that with normal subjects (healthy pooled control), a less than 50% increase in total rimegepant exposure was observed following a single 75 mg dose. The unbound AUC of rimegepant was 2.57-fold higher in subjects with severe renal impairment. Rimegepant has not been studied in patients with end-stage renal disease (CLcr <15 ml/min).

Preclinical data

Non-clinical data reveal no special hazard for rimegepant in humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, phototoxicity, reproduction or development toxicity, or carcinogenic potential.

Repeated dose toxicity

Rimegepant-related effects at higher doses in repeat-dose studies included hepatic lipidosis in mice and rats, intravascular hemolysis in rats and monkeys, and emesis in monkeys. These findings were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (≥12 times [mice] and ≥49 times [rats] for hepatic lipidosis, ≥95 times [rats] and ≥9 times [monkeys] for intravascular hemolysis, and ≥37 times for emesis [monkeys]).

Reproduction toxicity

In a fertility study in rats, rimegepant-related effects were noted only at the high dose of 150 mg/kg/day (decreased fertility and increased pre-implantation loss) that produced maternal toxicity and systemic exposures ≥95 times the maximum human exposure. Oral administration of rimegepant during organogenesis resulted in foetal effects in rats but not rabbits. In rats, decreased foetal body weight and increased incidence of foetal skeletal variations were observed only at the highest dose of 300 mg/kg/day that produced maternal toxicity at exposures approximately 200 times the maximum human exposure. Additionally, rimegepant had no effects on pre- and postnatal development in rats at doses up to 60 mg/kg/day (≥24 times the maximum human exposure) or on

growth, development, or reproductive performance of juvenile rats at doses up to 45 mg/kg/day (≥14 times the maximum human exposure).

Toxicity in juvenile animals

Rimegepant had no negative effects on the growth, development or reproductive function of juvenile rats administered rimegepant orally from postnatal Day 24 through postnatal Day 71 at doses up to 45 mg/kg/day (14 and 21 times the maximum human exposure in male and female rats, respectively).

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Special precautions for storage

Do not store above 30°C.

Keep the container in the original pack in order to protect the contents from moisture.

Keep out of the reach of children.

Authorisation number

69035

Packs

Oral lyophilisate 75 mg: 2, 8, 16.

Marketing authorisation holder

Pfizer AG, Zürich.

Information for healthcare professionals

Date of revision of the text

July 2023