เอกสารกำกับยา

NURTEC ODT™

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

NURTEC ODT

1.2 Strength

75 mg

1.3 Pharmaceutical Dosage Form

Orally disintegrating tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Active ingredient: Rimegepant sulfate.

2.2 Quantitative Declaration

Each NURTEC ODT orally disintegrating tablet contains 75 mg rimegepant.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orally disintegrating tablet (ODT): white to off-white, circular, and debossed with the symbol.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

NURTEC ODT is indicated for the

- Acute treatment of migraine with or without aura in adults.
- Preventive treatment of episodic migraine in adults.

4.2. Posology and Method of Administration

Posology

Acute treatment of migraine

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

Prophylaxis of migraine

The recommended dose is 75 mg rimegepant every other day.

The maximum dose per day is 75 mg rimegepant.

NURTEC ODT can be taken with or without meals.

Concomitant medicinal products

Another dose of rimegepant should be avoided within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 (see section 4.5).

Special populations

Elderly (aged 65 and over)

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 section 5.2).

Renal impairment

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 section 5.2). 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

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

Paediatric population

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

Method of administration

NURTEC ODT is for oral use.

NURTEC ODT 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.

4.3. Contraindications

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

4.4. Special Warnings and Precautions for Use

Hypersensitivity reactions, including dyspnoea and rash, have occurred in less than 1% of patients treated with rimegepant in clinical studies (see 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.

NURTEC ODT is not recommended:

- in patients with severe hepatic impairment (see section 4.2);
- in patients with end-stage renal disease (CLcr < 15 ml/min) (see section 4.2);
- for concomitant use with strong inhibitors of CYP3A4 (see section 4.5);
- for concomitant use with strong or moderate inducers of CYP3A4 (see section 4.5).

Medication overuse headache (MOH)

Overuse of any type of medicinal products 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.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Rimegepant is a substrate of CYP3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters (see section 5.2).

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 section 4.4). 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 hours should be avoided when it is concomitantly administered with moderate inhibitors of CYP3A4 (e.g., fluconazole) (see section 4.2).

CYP3A4 inducers

Inducers of CYP3A4 decrease plasma concentrations of rimegepant. Concomitant administration of NURTEC ODT 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 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 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 NURTEC ODT 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 two-fold).

4.6. Fertility, Pregnancy and Lactation

Pregnancy

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. 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 (see section 5.3). As a precautionary measure, it is preferable to avoid the use of NURTEC ODT during pregnancy.

Breast-feeding

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 NURTEC ODT and any potential adverse reactions on the breastfed infant from rimegepant or from the underlying maternal condition.

Fertility

Animal studies showed no clinically relevant impact on female and male fertility (see section 5.3).

4.7. Effects on Ability to Drive and Use Machines

NURTEC ODT has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable Effects

Summary of the safety profile

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, occurred in less than 1% of patients treated.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA system organ class in Table 1. The corresponding frequency category for each drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1: List of Adverse Reactions

System Organ Class	Adverse reaction	Frequency
Acute Treatment		
Immune system disorders	Hypersensitivity, including dyspnoea and severe rash	Uncommon
Gastrointestinal disorders	Nausea	Common
Prophylaxis		
Gastrointestinal disorders	Nausea	Common

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 received rimegepant for 12 months for acute or prophylactic treatment.

Description of selected adverse reactions

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.

4.9. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Analgesics, calcitonin gene-related peptide (CGRP) antagonists, 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.

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

Clinical efficacy: acute treatment

The efficacy of NURTEC ODT 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 hours after the initial treatment. Other forms of rescue medicinal products such as triptans were not allowed within 48 hours 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 hours after a single dose was statistically significantly greater in patients who received NURTEC

ODT compared to those who received placebo (Table 2). In addition, statistically significant effects of NURTEC ODT compared to placebo were demonstrated for the additional efficacy endpoints of pain relief at 2 hours, sustained pain freedom from 2 to 48 hours, use of rescue medication within 24 hours, and ability to function normally at 2 hours 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.

Table 2: Migraine Efficacy Endpoints for Acute Treatment Studies

	Study 1		**Study 2**		**Study 3**	
	NURTEC ODT 75 mg	**Placebo**	**Rimegepant 75 mg**	**Placebo**	**Rimegepant 75 mg**	**Placebo**
Pain Free at 2 hours						
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 hours						
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 hours						
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 hours						
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]		0.0181[b]		0.0130[b]

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

[a] Significant p-value in hierarchical testing

[b] Nominal p-value in hierarchical testing

MBS: most bothersome symptom

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

Figure 1: Percentage of Patients Achieving Pain Freedom within 2 Hours in Study 1

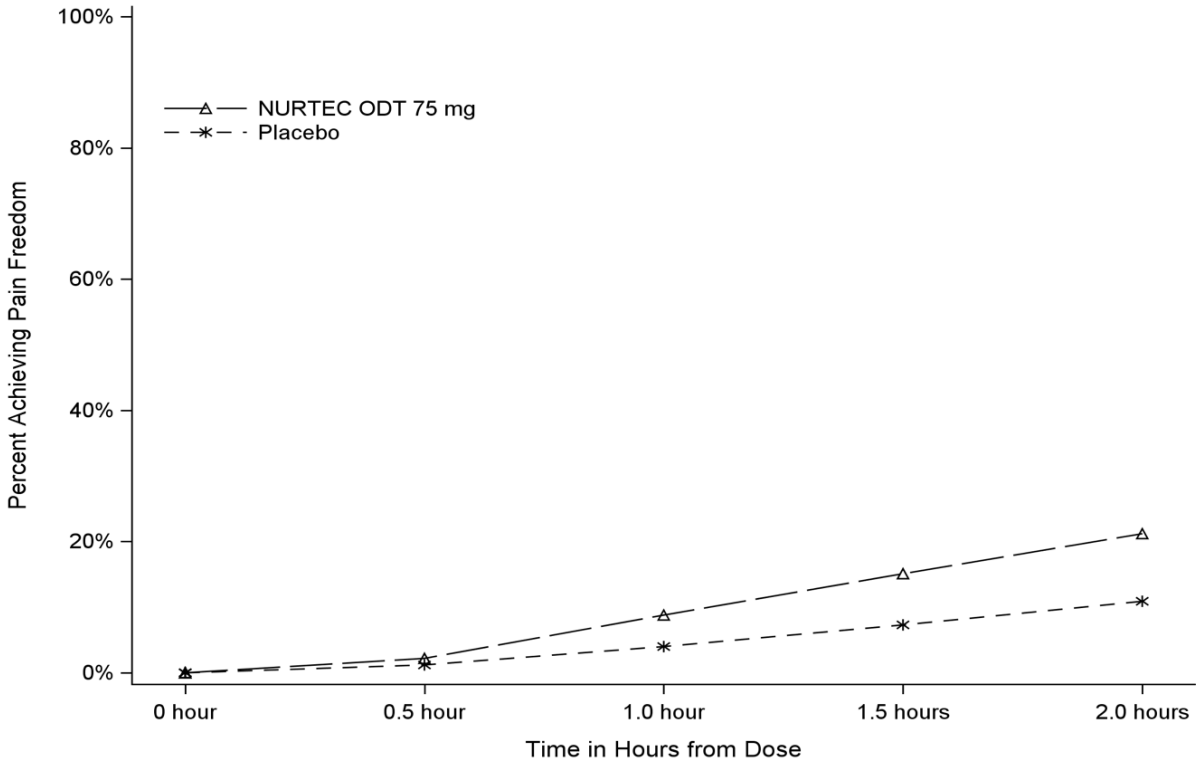
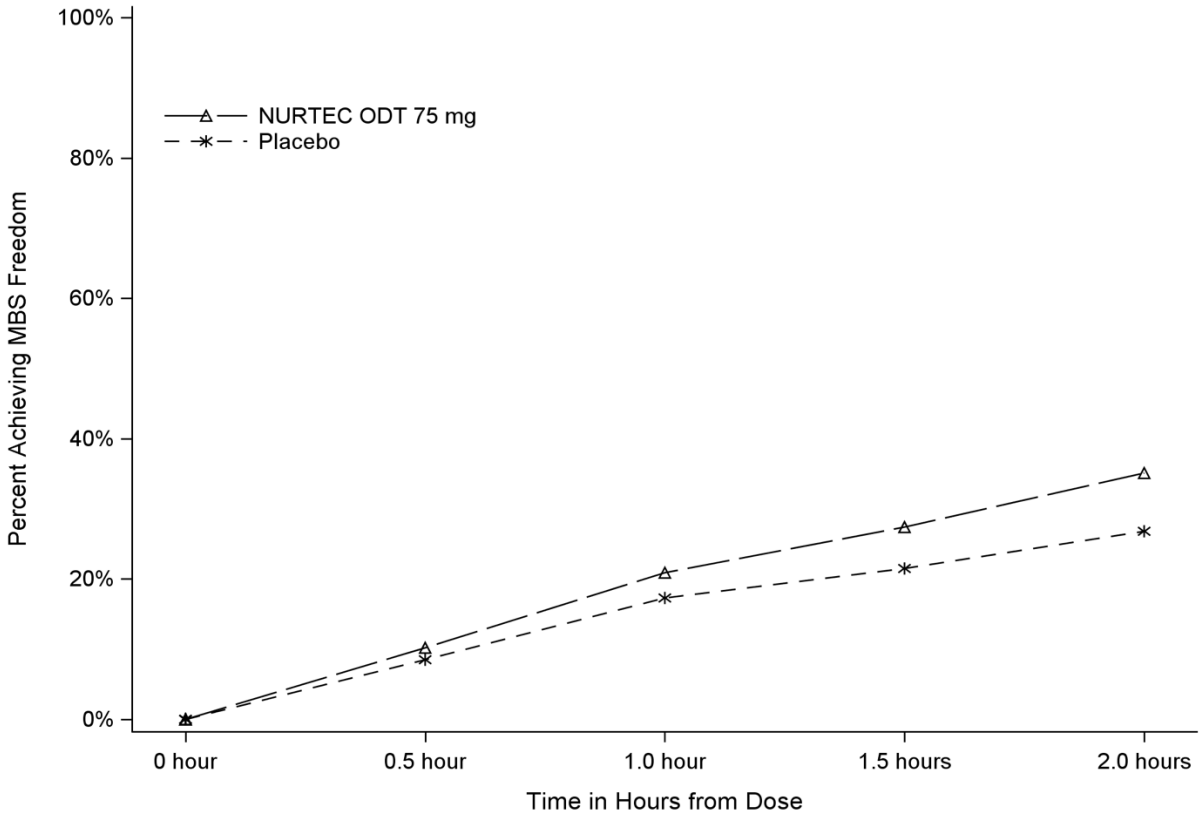


Figure 2 presents the percentage of patients achieving MBS freedom within 2 hours in Study 1.

Figure 2: Percentage of Patients Achieving MBS Freedom within 2 Hours in Study 1



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

Clinical efficacy: prophylaxis

The efficacy of rimegepant was evaluated as a prophylactic 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 rimegepant 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 $\geq$ 50% reduction from baseline in monthly moderate or severe migraine days.

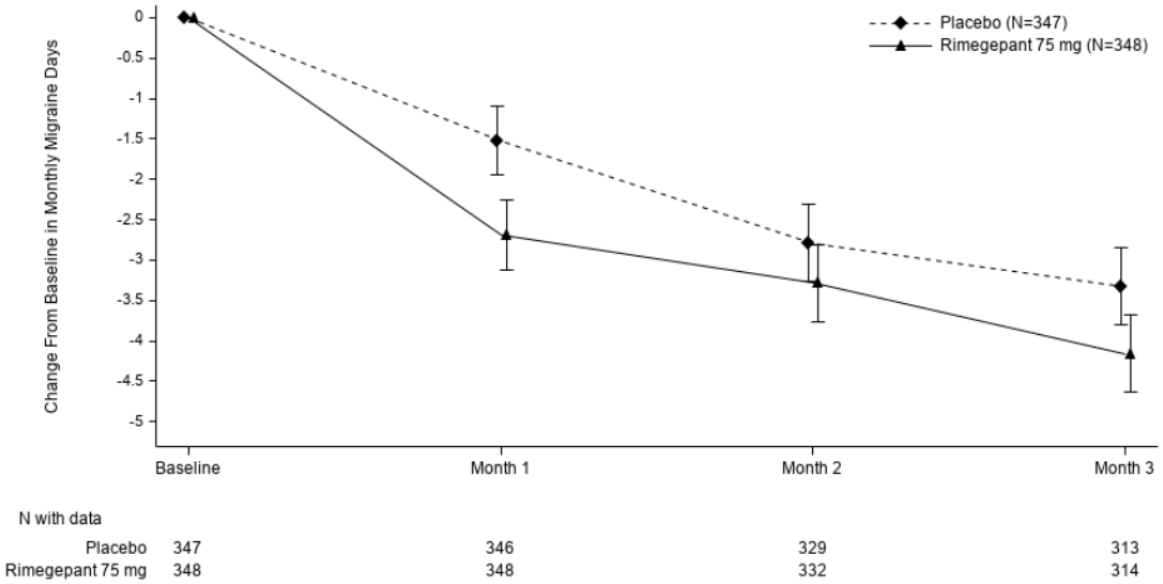
Rimegepant 75 mg dosed EOD demonstrated statistically significant improvements for key efficacy endpoints compared to placebo, as summarized in Table 3 and shown graphically in Figure 3.

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]	
$\geq$ 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

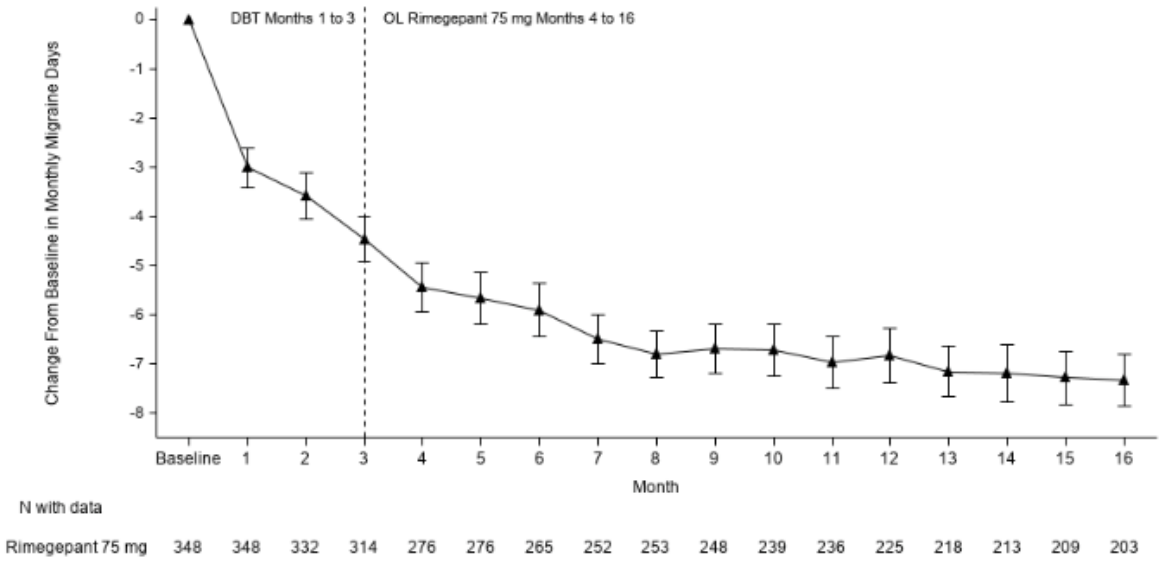
Figure 3: Change from Baseline in Monthly Migraine Days in Study 4



Long-term efficacy

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 (Figure 4). 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.

Figure 4: Longitudinal Plot of the Change in Mean Number of Monthly Migraine Days (MMDs) from the Observation Period Over Time during Double-Blind Treatment (Months 1 to 3) and during Treatment with Open-label Rimegepant (Months 4 to 16)



5.2. Pharmacokinetic Properties

Absorption

Following oral administration, rimegepant is absorbed with the maximum concentration at 1.5 hours. 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 hours. 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%.

Biotransformation

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.

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.

Elimination

The elimination half-life of rimegepant is approximately 11 hours 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%).

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 section 4.5).

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.

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.

Age, sex, weight, race, ethnicity

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

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).

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.

5.3. Preclinical Safety Data

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

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 ($\geq$ 12 times [mice] and $\geq$ 49 times [rats] for hepatic lipidosis, $\geq$ 95 times [rats] and $\geq$ 9 times [monkeys] for intravascular hemolysis, and $\geq$ 37 times for emesis [monkeys]).

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 $\geq$ 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 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 ($\geq$ 24 times the maximum human exposure) or on growth, development, or reproductive performance of juvenile rats at doses up to 45 mg/kg/day ($\geq$ 14 times the maximum human exposure).

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Gelatin
Mannitol
Mint flavour
Sucralose

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

4 years

6.4. Special Precautions for Storage

Do not store above 30 °C.

Store in the original package in order to protect from moisture.

6.5. Nature and Contents of Container

Unit dose blisters made of polyvinyl chloride (PVC), oriented polyamide (OPA) and aluminium foil and sealed with a peelable aluminum foil.

Pack sizes:

Unit dose 2 x 1 oral disintegrating tablet.

Unit dose 8 x 1 oral disintegrating tablet.

Unit dose 16 x 1 oral disintegrating tablet.

Not all pack sizes may be marketed.

7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited

8. MARKETING AUTHORIZATION NUMBERS

1C 15089/66 (NC)

9. DATE OF AUTHORIZATION

25 December 2023

10. DATE OF REVISION OF THE TEXT

11 September 2023