

NURTEC ODT- rimegepant sulfate tablet, orally disintegrating

Biohaven Pharmaceuticals, Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NURTEC[®] ODT safely and effectively. See full prescribing information for NURTEC ODT.

NURTEC ODT (rimegepant) orally disintegrating tablets, for sublingual or oral use

Initial U.S. Approval: 2020

-----RECENT MAJOR CHANGES-----

Indications and Usage (1.2)	5/2021
Dosage and Administration (2.1, 2.2)	5/2021
Dosage and Administration (2.6)	12/2021

-----INDICATIONS AND USAGE-----

NURTEC ODT is a calcitonin gene-related peptide receptor antagonist indicated for the:

- acute treatment of migraine with or without aura in adults (1.1)
- preventive treatment of episodic migraine in adults (1.2)

-----DOSAGE AND ADMINISTRATION-----

- Recommended dosage for acute treatment of migraine: 75 mg taken orally, as needed. (2.1)
- The safety of using more than 18 doses in a 30-day period has not been established. (2.1)
- Recommended dosage for preventive treatment of episodic migraine: 75 mg taken orally every other day. (2.2)
- The maximum dose in a 24-hour period is 75 mg. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

NURTEC ODT orally disintegrating tablets: 75 mg (3)

-----CONTRAINDICATIONS-----

Patients with a history of hypersensitivity reaction to rimegepant, NURTEC ODT, or to any of its components. (4)

-----WARNINGS AND PRECAUTIONS-----

Hypersensitivity Reactions: If a serious hypersensitivity reaction occurs, discontinue NURTEC ODT and initiate appropriate therapy. Severe hypersensitivity reactions have included dyspnea and rash, and can occur days after administration. (5.1)

-----ADVERSE REACTIONS-----

Acute treatment of migraine: the adverse reaction reported in $\geq 1\%$ of patients treated with NURTEC ODT is nausea. (6.1)

Preventive treatment of episodic migraine: adverse reactions reported in $\geq 2\%$ for rimegepant and $\geq 1\%$ higher than placebo are nausea and abdominal pain/dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biohaven Pharmaceuticals Inc. at 1-833-4BIOHVN or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Strong CYP3A4 Inhibitors: Avoid concomitant administration. (7.1)
- Moderate CYP3A4 Inhibitors: Avoid another dose within 48 hours when administered with a moderate

- CYP3A4 inhibitor. (7.1)
- Strong and Moderate CYP3A Inducers: Avoid concomitant administration. (7.2)
- Potent Inhibitors of P-gp: Avoid another dose of NURTEC ODT within 48 hours when administered with a potent P-gp inhibitor. (7.3)

----- **USE IN SPECIFIC POPULATIONS** -----

- Exposures were significantly higher in subjects with severe hepatic impairment. Avoid use in patients with severe hepatic impairment (Child-Pugh C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Treatment of Migraine

NURTEC ODT is indicated for the acute treatment of migraine with or without aura in adults .

1.2 Preventive Treatment of Episodic Migraine

NURTEC ODT is indicated for the preventive treatment of episodic migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing for Acute Treatment of Migraine

The recommended dose of NURTEC ODT is 75 mg taken orally, as needed.

The maximum dose in a 24-hour period is 75 mg. The safety of using more than 18 doses in a 30-day period has not been established.

2.2 Recommended Dosing for Preventive Treatment of Episodic Migraine

The recommended dosage of NURTEC ODT is 75 mg taken orally every other day.

2.3 Administration Information

Instruct the patient on the following administration instructions:

- Use dry hands when opening the blister pack.
- Peel back the foil covering of one blister and gently remove the orally disintegrating tablet (ODT). Do not push the ODT through the foil.
- As soon as the blister is opened, remove the ODT and place on the tongue; alternatively, the ODT may be placed under the tongue.
- The ODT will disintegrate in saliva so that it can be swallowed without additional liquid.
- Take the ODT immediately after opening the blister pack. Do not store the ODT outside the blister pack for future use.

2.4 Concomitant Administration with Strong or Moderate CYP3A4 Inhibitors

Avoid concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4. Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].


2.5 Concomitant Administration with Strong or Moderate CYP3A Inducers

Avoid concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A, which may lead to loss of efficacy of NURTEC ODT [see *Drug Interactions (7.2)*, *Clinical Pharmacology (12.3)*].

2.6 Concomitant Administration with Potent Inhibitors of P-gp

Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with potent inhibitors of P-gp [see *Drug Interactions (7.3)*, *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Orally disintegrating tablets: white to off-white, circular, and debossed with the symbol , each containing 75 mg of rimegepant.

4 CONTRAINDICATIONS

NURTEC ODT is contraindicated in patients with a history of hypersensitivity reaction to rimegepant, NURTEC ODT, or any of its components. Delayed serious hypersensitivity has occurred [see *Warnings and Precautions (5.1)*].

5 WARNING AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including dyspnea and rash, have occurred with NURTEC ODT in clinical studies. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred. If a hypersensitivity reaction occurs, discontinue NURTEC ODT and initiate appropriate therapy [see *Contraindications (4)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity Reactions [see *Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Acute Treatment of Migraine

The safety of NURTEC ODT for the acute treatment of migraine in adults has been evaluated in a randomized, double-blind, placebo-controlled trial (Study 1) in 682 patients with migraine who received one 75 mg dose of NURTEC ODT [see *Clinical Studies (14)*]. Approximately 85% were female, 74% were White, 21% were Black, and 17% were Hispanic or Latino. The mean age at study entry was 40 years (range 18-75 years of age).

Long-term safety was assessed in an open-label extension study using a different oral dosage form of rimegepant. That study evaluated 1,798 patients, dosing intermittently for up to one year, including 1,131 patients who were exposed to rimegepant 75 mg for at least 6 months, and 863 who were exposed for at least one year, all of whom treated an average of at least two migraine attacks per month.

The most common adverse reaction in Study 1 was nausea (2% in patients who received NURTEC ODT compared to 0.4% of patients who received placebo).

Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Preventive Treatment of Episodic Migraine

The safety of NURTEC ODT for the preventive treatment of episodic migraine in adults has been established in a randomized, double-blind, placebo-controlled trial with an open-label extension (Study 2) using a different oral dosage form of rimegepant [see *Clinical Studies (14)*]. In the 12-week, double-blind treatment period, 370 patients with migraine received one 75 mg dose of rimegepant every other day. Approximately 81% were female, 80% were White, 17% were Black, and 28% were Hispanic or Latino. The mean age at study entry was 41 years (range 18-74 years of age). Long-term safety was assessed in an open-label extension study that included 603 patients who were treated for up to one year. Overall, 527 patients were exposed to rimegepant 75 mg for at least 6 months, and 311 were exposed for at least one year.

The most common adverse reactions (occurring in at least 2% of rimegepant-treated patients and at a frequency of at least 1% higher than placebo) in Study 2 were nausea (2.7% in patients who received rimegepant compared with 0.8% of patients who received placebo) and abdominal pain/dyspepsia (2.4% in patients who received rimegepant compared with 0.8% of patients who received placebo).

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

Concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 results in a significant increase in rimegepant exposure. Avoid concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 [see *Clinical Pharmacology (12.3)*].

Concomitant administration of NURTEC ODT with moderate inhibitors of CYP3A4 may result in increased exposure of rimegepant. Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 [see *Clinical Pharmacology (12.3)*].

7.2 CYP3A Inducers

Concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A can result in a significant reduction in rimegepant exposure, which may lead to loss of efficacy of NURTEC ODT. Avoid concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A [see *Clinical Pharmacology (12.3)*].

7.3 P-gp Inhibitors

Concomitant administration of NURTEC ODT with potent inhibitors of P-gp (e.g., amiodarone, cyclosporine, lapatinib, quinidine, ranolazine) may result in increased exposure of rimegepant. Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with potent inhibitors of P-gp [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NURTEC ODT during pregnancy. For more information, healthcare providers or patients are encouraged to contact: 1-877-366-0324, email nurtecpregnancyregistry@ppd.com, or visit nurtecpregnancyregistry.com.

Risk Summary

There are no adequate data on the developmental risk associated with the use of NURTEC ODT in pregnant women. In animal studies, oral administration of rimegepant during organogenesis resulted in adverse effects on development in rats (decreased fetal body weight and increased incidence of fetal variations) at exposures greater than those used clinically and which were associated with maternal toxicity. The evaluation of developmental effects following oral administration of rimegepant throughout pregnancy and lactation was inadequate (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated rate of major birth defects (2.2 to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

Oral administration of rimegepant (0, 10, 60, or 300 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreased fetal body weight and an increased

incidence of fetal variations at the highest dose tested (300 mg/kg/day), which was associated with maternal toxicity. Plasma exposures (AUC) at the no-effect dose (60 mg/kg/day) for adverse effects on embryofetal development were approximately 45 times that in humans at the maximum recommended human dose (MRHD) of 75 mg/day.

Oral administration of rimegepant (0, 10, 25, or 50 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in no adverse effects on embryofetal development. The highest dose tested (50 mg/kg/day) was associated with plasma exposures (AUC) approximately 10 times that in humans at the MRHD.

The prenatal and postnatal development study in rats, in which rimegepant (0, 10, 25, or 60 mg/kg/day) was orally administered throughout gestation and lactation, was inadequate to assess for adverse effects of rimegepant during these periods of development.

8.2 Lactation

There are no data on the presence of rimegepant or its metabolites in human milk, the effects of rimegepant on the breastfed infant, or the effects of rimegepant on milk production. There are no animal data on the excretion of rimegepant in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NURTEC ODT and any potential adverse effects on the breastfed infant from NURTEC ODT or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects. Clinical studies of NURTEC ODT did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dosage adjustment of NURTEC ODT is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Plasma concentrations of rimegepant were significantly higher in subjects with severe (Child-Pugh C) hepatic impairment. Avoid use of NURTEC ODT in patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

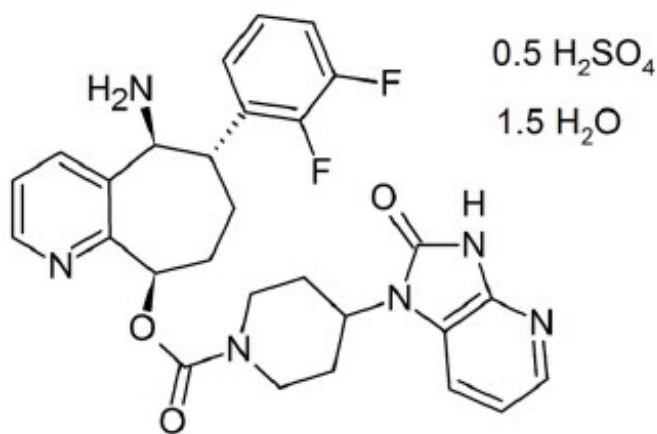
No dosage adjustment of NURTEC ODT is required in patients with mild, moderate, or severe renal impairment. NURTEC ODT has not been studied in patients with end-stage renal disease and in patients on dialysis. Avoid use of NURTEC ODT in patients with end-stage renal disease (CL_{cr} < 15 mL/min) [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is limited clinical experience with NURTEC ODT overdose. Treatment of an overdose of NURTEC ODT 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 [see *Clinical Pharmacology* (12.3)] .

11 DESCRIPTION

NURTEC ODT contains rimegepant sulfate, a calcitonin gene-related peptide receptor antagonist. Rimegepant sulfate is described chemically as (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-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxylate hemisulfate sesquihydrate and its structural formula is:



Its empirical formula is C₂₈H₂₈F₂N₆O₃ · 0.5 H₂SO₄ · 1.5 H₂O, representing a molecular weight of 610.63. Rimegepant free base has a molecular weight of 534.56. Rimegepant sulfate is a white to off-white, crystalline solid that is slightly soluble in water.

NURTEC ODT (orally disintegrating tablets) is for sublingual or oral use and contains 85.7 mg rimegepant sulfate, equivalent to 75 mg rimegepant free base, and the following inactive ingredients: benzyl alcohol, eucalyptol, gelatin, limonene, mannitol, menthol, menthone, menthyl acetate, sucralose, and vanillin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rimegepant is a calcitonin gene-related peptide receptor antagonist.

12.2 Pharmacodynamics

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

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.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Absorption

Following oral administration of NURTEC ODT, rimegepant is absorbed with the maximum concentration at 1.5 hours. The absolute oral bioavailability of rimegepant is approximately 64%.

Effects of Food

Following administration of NURTEC ODT under fed conditions with a high-fat or low-fat meal, T_{max} was delayed by approximately 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%. NURTEC ODT was administered without regard to food in clinical safety and efficacy studies. The impact of the reduction in rimegepant exposure because of administration with food on its efficacy is unknown.

Distribution

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

Elimination

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.

Excretion

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%).

Specific Populations

Renal Impairment

In a dedicated clinical study comparing the pharmacokinetics of rimegepant in subjects with mild (estimated creatinine clearance [CL_{cr}] 60-89 mL/min), moderate (CL_{cr} 30-59 mL/min), and severe (CL_{cr} 15-29 mL/min) renal impairment to that with normal subjects (healthy matched control), the exposure of rimegepant following single 75 mg dose was approximately 40% higher in subjects with moderate renal impairment. However, there was no clinically meaningful difference in the exposure of rimegepant in subjects with severe renal impairment compared to subjects with normal renal function (CL_{cr} ≥ 90 mL/min). NURTEC ODT has not been studied in patients with end-stage renal disease (CL_{cr} < 15 mL/min) [see *Use in Specific Populations* (8.7)].

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 (C_{max} and AUC) following single 75 mg dose was approximately 2-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 [see *Use in Specific Populations (8.6)*].

Other Specific Populations

No clinically significant differences in the pharmacokinetics of rimegepant were observed based on age, sex, race/ethnicity, body weight, or CYP2C9 genotype [see *Clinical Pharmacology (12.5)*].

Drug Interaction Studies

In Vitro Studies

- Enzymes

Rimegepant is a substrate of CYP3A4 and CYP2C9 (see *In Vivo 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.

- Transporters

Rimegepant is a substrate of P-gp and BCRP (see *In Vivo Studies*) .

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. In a dedicated interaction study, concomitant administration of 75 mg rimegepant at steady state with metformin, a MATE1 transporter substrate, at steady state resulted in no clinically significant impact on either metformin pharmacokinetics or on glucose utilization. No clinical drug interactions are expected for NURTEC ODT with OATP1B3 or OCT2, at clinically relevant concentrations.

In Vivo Studies

CYP3A4 Inhibitors

In a dedicated drug interaction study, concomitant administration of 75 mg rimegepant (single dose) with itraconazole, a strong CYP3A4 inhibitor, at steady state resulted in increased exposures of rimegepant (AUC by 4-fold and C_{max} by ~1.5-fold) [see *Drug Interactions (7.1)*]. No dedicated drug interaction study was conducted to assess the effect of concomitant administration of a weak inhibitor of CYP3A4 on the pharmacokinetics of rimegepant. The concomitant administration of rimegepant with a moderate inhibitor of CYP3A4 may increase rimegepant exposures (AUC) by less than 2-fold [see *Drug Interactions (7.1)*]. Concomitant administration of rimegepant with a weak

inhibitor of CYP3A4 is not expected to have a clinically significant impact on rimegepant exposures.

CYP3A Inducers

In a dedicated drug interaction study, concomitant administration of 75 mg rimegepant (single dose) with rifampin, a strong CYP3A4 inducer, at steady state resulted in decreased exposures of rimegepant (AUC by 80% and C_{max} by 64%), which may lead to loss of efficacy [see *Drug Interactions (7.2)*]. No dedicated drug interaction study was conducted to assess the effect of concomitant administration of a moderate or weak inducer of CYP3A4 on the pharmacokinetics of rimegepant. Since rimegepant is a moderately sensitive substrate for CYP3A4, drugs that are moderate inducers of CYP3A4 can also cause significant reduction in rimegepant exposure resulting in loss of efficacy [see *Drug Interactions (7.2)*]. Clinically significant interaction is not expected with concomitant administration of weak inducers of CYP3A4 and rimegepant.

CYP2C9 Inhibitors

In a dedicated drug interaction study, concomitant administration of 75 mg rimegepant (single dose) with fluconazole, a combined moderate CYP3A4 and CYP2C9 inhibitor, resulted in increased exposures of rimegepant (AUC by 1.8-fold) with no relevant effect on C_{max} . Rimegepant is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9. Increase in the exposure of rimegepant can be attributed to combined inhibition of CYP2C9 and CYP3A4 with fluconazole administration suggesting a minor contribution from CYP2C9. Thus, CYP2C9 inhibition alone is not expected to significantly affect rimegepant exposures.

P-gp and BCRP Inhibitors

In a dedicated drug interaction study, concomitant administration of NURTEC ODT with cyclosporine (a potent P-gp and BCRP inhibitor) and with quinidine (a potent P-gp inhibitor) resulted in an increase of similar magnitude in rimegepant exposure (AUC and C_{max} by 1.6 and 1.4 fold with cyclosporine, and by 1.6 and 1.7 fold with quinidine, respectively) [see *Drug Interactions (7.3)*]. Therefore, concomitant administration of NURTEC ODT with BCRP inhibitors is not expected to have a clinically significant impact on rimegepant exposures.

Other Drugs: No significant pharmacokinetic interactions were observed when rimegepant was concomitantly administered with oral contraceptives (norelgestromin, ethinyl estradiol), midazolam (a sensitive CYP3A4 substrate), metformin (a MATE1 substrate), or sumatriptan [see *Clinical Pharmacology (12.2)*].

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Rimegepant C_{max} and AUC_{0-inf} were similar in CYP2C9 intermediate metabolizers (i.e., *1/*2, *2/*2, *1/*3, n=43) as compared to normal metabolizers (i.e., *1/*1, N=72). Adequate PK data are not available from CYP2C9 poor metabolizers (i.e., *2/*3). Since the contribution of CYP2C9 to rimegepant metabolism is considered minor, CYP2C9 polymorphism is not expected to significantly affect its exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of rimegepant to Tg.rasH2 mice (0, 10, 100, or 300 mg/kg/day) for 26 weeks and to rats (0, 5, 20, or 45 mg/kg/day) for 91-100 weeks resulted in no evidence of drug-induced tumors in either species. In rats, the plasma exposure (AUC) at the highest dose tested (45 mg/kg/day) was approximately 30 times that in humans at the maximum recommended human dose (MRHD) of 75 mg/day.

Mutagenesis

Rimegepant was negative in in vitro (bacterial reverse-mutation, chromosomal aberration in Chinese hamster ovary cells) and in vivo (rat micronucleus) assays.

Impairment of Fertility

Oral administration of rimegepant (0, 30, 60, or 150 mg/kg/day) to male and female rats prior to and during mating and continuing in females to gestation day (GD) 7 resulted in uterine atrophy at all doses and reduced fertility at the highest dose tested. In a second fertility study testing lower doses (0, 5, 15, or 25 mg/kg/day), no adverse effects on fertility, uterine histopathology, or early embryonic development were observed. The no-effect dose for impairment of fertility and early embryonic development in rats (25 mg/kg/day) was associated with plasma drug exposures (AUC) approximately 15 times that in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Acute Treatment of Migraine

The efficacy of NURTEC ODT for the acute treatment of migraine with and without aura in adults was demonstrated in a randomized, double-blind, placebo-controlled trial: Study 1 (NCT03461757). Patients in the study were randomized to receive 75 mg of NURTEC ODT (N=732) or placebo (N=734). Patients were instructed to treat a migraine of moderate to severe headache pain intensity. Rescue medication (i.e., NSAIDs, acetaminophen, and/or an antiemetic) was allowed 2 hours after the initial treatment. Other forms of rescue medication such as triptans were not allowed within 48 hours of initial treatment. Approximately 14% of patients were taking preventive medications for migraine at baseline. None of the patients in Study 1 were on concomitant preventive medication that act on the CGRP pathway.

The primary efficacy analyses were conducted in patients who treated a migraine with moderate to severe pain. NURTEC ODT 75 mg demonstrated an effect on pain freedom and most bothersome symptom (MBS) freedom at two hours after dosing, compared to placebo. Pain freedom was defined as a reduction of moderate or severe headache pain to no headache pain, and 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 two hours after a single dose was statistically significantly greater in patients who received NURTEC ODT compared to those who received placebo (Table 1).

Table 1: Efficacy Endpoints for the Acute Treatment of Migraine in Study 1

	Study 1	
	NURTEC ODT 75 mg	Placebo
Pain Free at 2 hours		
n/N *	142/669	74/682
% Responders	21.2	10.9
Difference from placebo (%)	10.3	
p-value		<0.001
MBS Free at 2 hours		
n/N *	235/669	183/682
% Responders	35.1	26.8
Difference from placebo (%)	8.3	
p-value		0.001

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

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

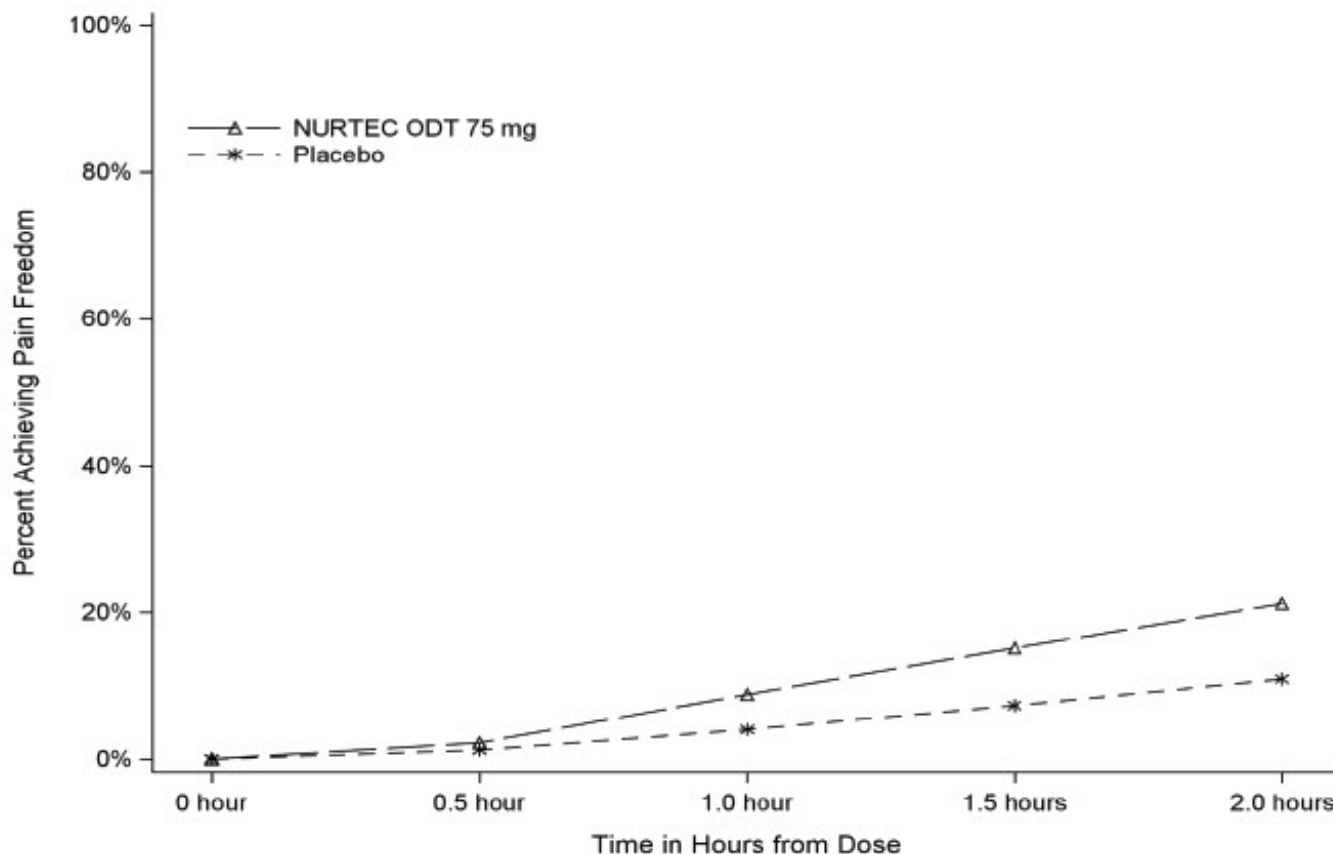
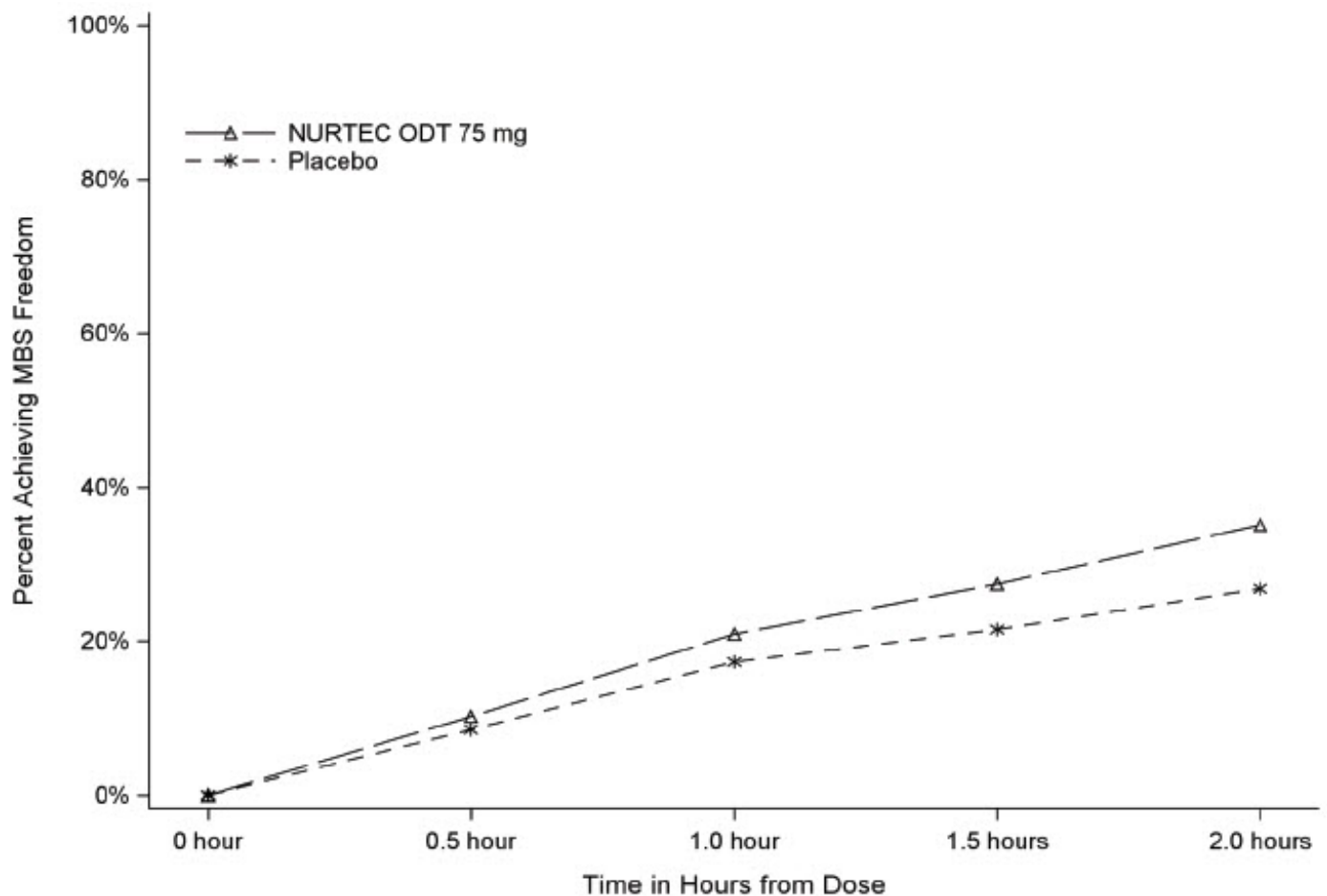


Figure 2 presents the percentage of patients achieving MBS freedom within 2 hours in Study 1.

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

Study 1



In Study 1, 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 2-48 hours, use of rescue medication within 24 hours, and the percentage of patients reporting normal function at two hours after dosing (Table 2). Pain relief was defined as a reduction in migraine pain from moderate or severe severity to mild or none. The measurement of the percentage of patients reporting normal function at two hours after dosing was derived from a single item questionnaire, asking patients to select one response on a 4-point scale; normal function, mild impairment, severe impairment, or required bedrest.

Table 2: Additional Acute Treatment of Migraine Efficacy Endpoints in Study 1

	Study 1	
	NURTEC ODT 75 mg	Placebo
Pain Relief at 2 hours		
n/N *	397/669	295/682
% Responders	59.3	43.3
Difference from placebo	16.1	
p-value		<0.001
Sustained Pain Freedom 2-48 hours		
n/N *	90/669	37/682
% Responders	13.5	5.4

Difference from placebo	8.0	
p-value		<0.001
Use of Rescue Medication within 24 hours †		
n/N *	95/669	199/682
% Responders	14.2	29.2
Difference from placebo	-15.0	
p-value		<0.001
Percentage of Patients Reporting Normal Function at 2 hours		
n/N *	255/669	176/682
% Responders	38.1	25.8
Difference from placebo	12.3	
p-value		<0.001

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

† This analysis includes only the use of NSAIDs, acetaminophen, or antiemetics, within 24 hours post-dose; the use of triptans, or other acute migraine medication, was not allowed.

The incidence of photophobia and phonophobia was reduced following administration of NURTEC ODT 75 mg as compared to placebo.

14.2 Preventive Treatment of Episodic Migraine

The efficacy of NURTEC ODT for the preventive treatment of episodic migraine in adults was demonstrated in one randomized, double-blind, placebo-controlled trial of a different oral dosage form of rimegepant (Study 2; NCT03732638).

Study 2 enrolled adult patients with at least a 1-year history of migraine (with or without aura). 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 trial. Patients were randomized to receive every other day dosing of rimegepant 75 mg (N=373) or placebo (N=374) for 12 weeks. Patients were allowed to use acute headache treatments (i.e., triptans, NSAIDs, acetaminophen, antiemetics, muscle relaxants, and aspirin) as needed. Approximately 10% of patients were taking one preventive medication for migraine at baseline. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either the acute or preventive treatment of migraine.

The study excluded patients with myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack within six months of screening.

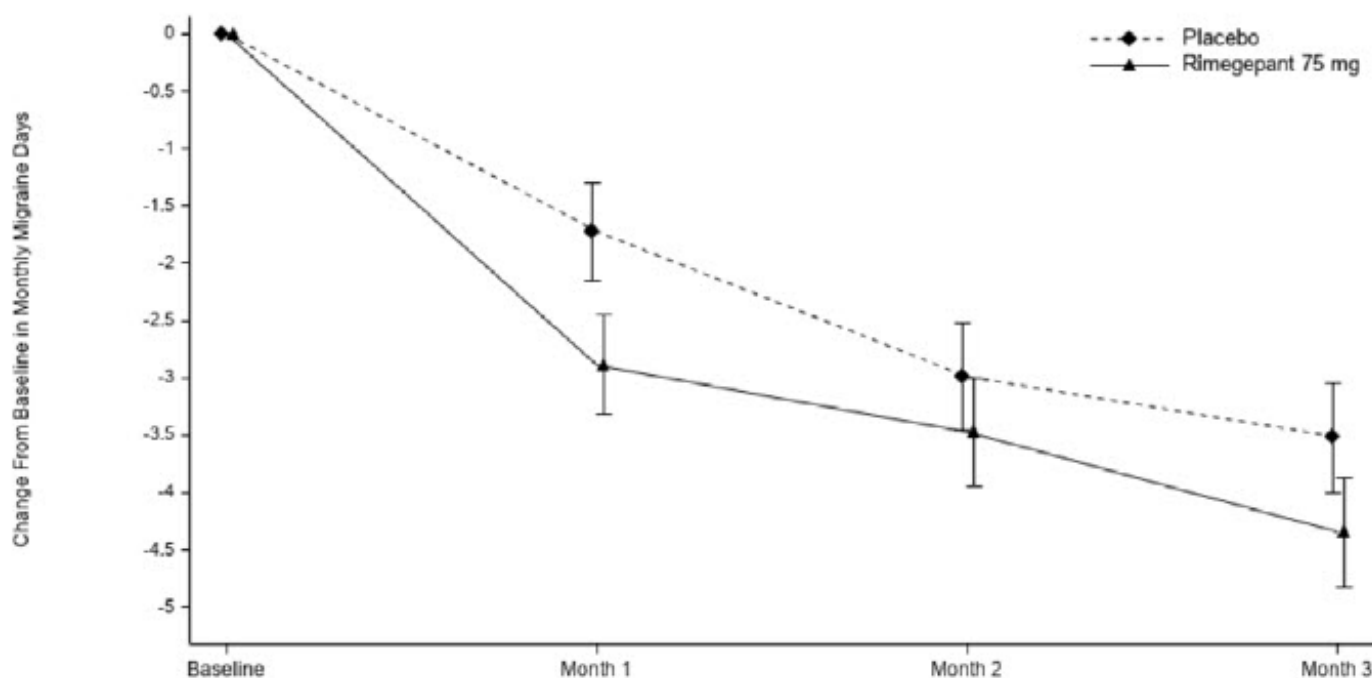
The primary efficacy endpoint for Study 2 was the change from baseline in the mean number of monthly migraine days (MMDs) during Weeks 9 through 12 of the double-blind treatment phase.

The percentage of patients who achieved at least a 50% reduction from baseline in moderate to severe MMDs during Weeks 9 through 12 of the double-blind treatment phase compared to placebo was also evaluated. Rimegepant 75 mg dosed every other day demonstrated statistically significant improvements for these efficacy endpoints compared to placebo, as summarized in Table 3.

Table 3: Efficacy Endpoints for the Preventive Treatment of Episodic Migraine in Study 2

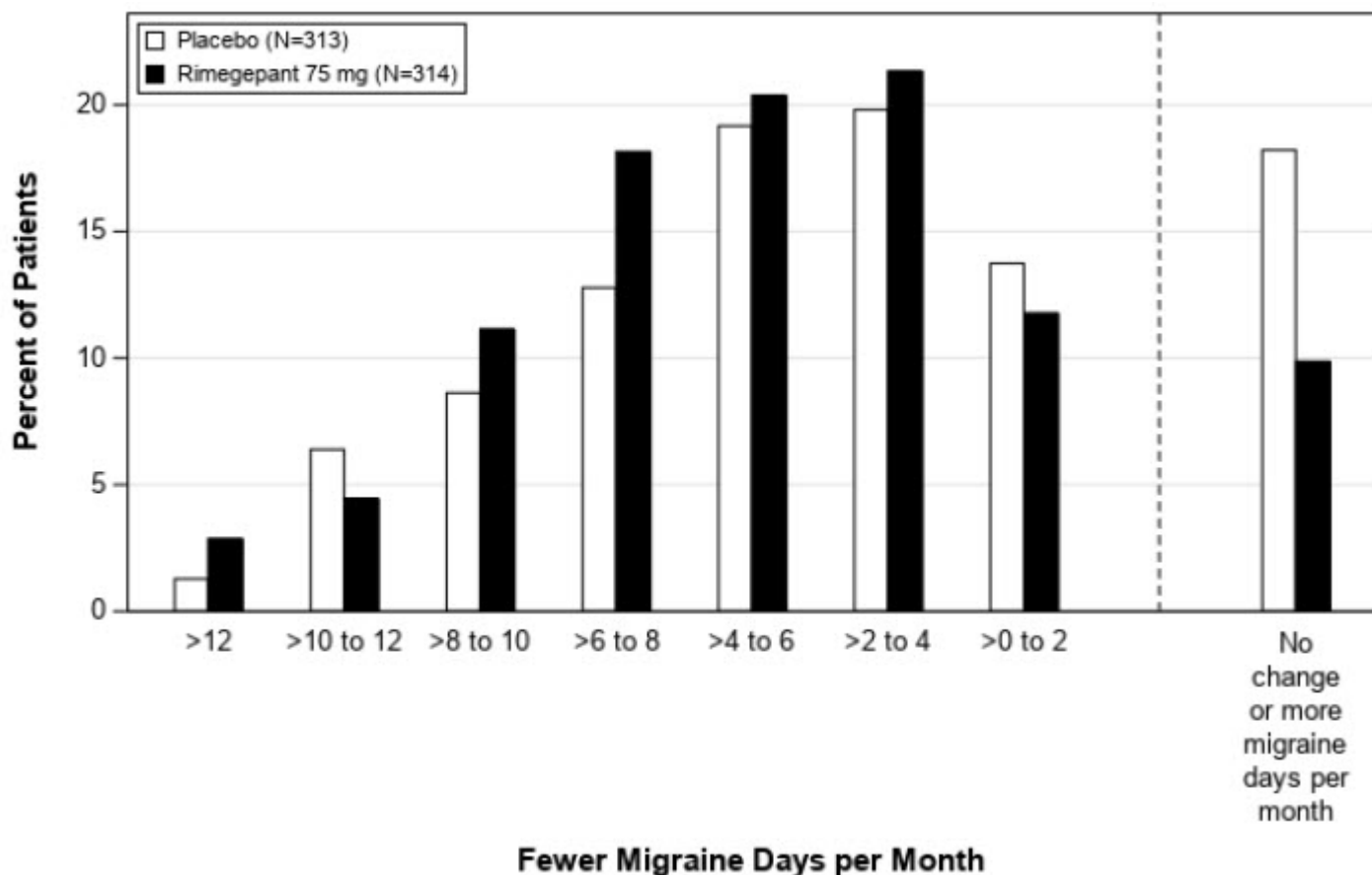
	Rimegepant 75 mg Every Other Day	Placebo Every Other Day
Monthly Migraine Days (MMD), Weeks 9-12	N=348	N=347
Change from baseline	-4.3	-3.5
Change from placebo	-0.8	
p-value	0.010	
≥ 50% Responders (Moderate to Severe MMDs), Weeks 9-12	N=348	N=347
% Responders	49.1	41.5
Difference from placebo	7.6	
p-value	0.044	

Figure 3: Change from Baseline in Monthly Migraine Days in Study 2 ^a



^aLeast-square means and 95% confidence intervals are presented.


Figure 4: Distribution of Change from Baseline in Mean Monthly Migraine Days at Month 3 by Treatment Group in Study 2 ^a



^aFigure excludes patients with missing data.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NURTEC ODT 75 mg orally disintegrating tablets are white to off-white, circular, debossed with the symbol , and supplied in cartons containing a blister pack of 8 orally disintegrating tablets. Each ODT contains 75 mg rimegepant.

NDC: 72618-3000-2

16.2 Storage and Handling

Store NURTEC ODT at controlled room temperature, 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Handling of Orally Disintegrating Tablets Packaging

Instruct patients not to remove the blister from the outer aluminum pouch until ready to use the orally disintegrating tablet inside [see Dosage and Administration (2.3)].

Hypersensitivity Reactions

Inform patients about the signs and symptoms of hypersensitivity reactions and that these reactions can occur days after administration of NURTEC ODT. Advise patients to contact their healthcare provider immediately if signs or symptoms of hypersensitivity reactions occur [see *Warnings and Precautions (5.1)*].

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NURTEC ODT during pregnancy. Encourage participation and advise patients about how they may enroll in the registry [see *Use in Specific Populations (8.1)*].

Manufactured for:

Biohaven Pharmaceuticals, Inc.

New Haven, CT 06510 USA

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PATIENT INFORMATION

PATIENT INFORMATION

NURTEC® ODT (NUR-tek)

(rimegepant)

orally disintegrating tablets (ODT), for sublingual or oral use

What is NURTEC ODT?

NURTEC ODT is a prescription medicine used in adults for the:

- acute treatment of migraine attacks with or without aura
- preventive treatment of episodic migraine

It is not known if NURTEC ODT is safe and effective in children.

Do not take NURTEC ODT if you are:

- allergic to rimegepant, NURTEC ODT, or any of the ingredients in NURTEC ODT.

See the end of this leaflet for a complete list of ingredients in NURTEC ODT.

Before you take NURTEC ODT, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if NURTEC ODT will harm your unborn baby. There is a pregnancy exposure registry for women who take NURTEC ODT during pregnancy. The study is named MONITOR (Migraine Observational NURTEC Pregnancy Registry). A registry is a study. The purpose of this registry is to collect information about your health and the health of your baby. Your healthcare provider can help you enroll in this registry. You may also enroll yourself or get more information about the registry by calling 1-877-366-0324, emailing nurtecpregnancyregistry@ppd.com, or by visiting

nurtecpregnancyregistry.com.

- are breastfeeding or plan to breastfeed. It is not known if NURTEC ODT passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take NURTEC ODT?

- Take NURTEC ODT exactly how your healthcare provider tells you to.
- For the acute treatment of migraine attacks when they occur, NURTEC ODT can be taken 1 time each day as needed. You should not take more than 1 tablet in 24 hours.
 - It is not known if it is safe to take more than 18 doses of NURTEC ODT in 30 days.
- For the preventive treatment of episodic migraine, take NURTEC ODT 1 time every other day.
- To take NURTEC ODT:
 - Use dry hands when opening the blister pack.
 - Peel back the foil covering of one blister and gently remove NURTEC ODT. Do not push NURTEC ODT through the foil.
 - As soon as the blister is opened, remove NURTEC ODT and place on or under the tongue.
 - NURTEC ODT will dissolve and no drink or water is needed.
 - Take NURTEC ODT immediately after opening the blister pack. Do not store NURTEC ODT outside the blister pack for future use.
- If you take too much NURTEC ODT, go to the nearest emergency room right away.

What are the possible side effects of NURTEC ODT?

NURTEC ODT may cause serious side effects including:

- **Allergic reactions.** Allergic reactions, including trouble breathing and rash, can happen after you take NURTEC ODT. This can happen days after you take NURTEC ODT. Call your healthcare provider or get emergency help right away if you have any of the following symptoms, which may be part of an allergic reaction:
 - Swelling of the face, mouth, tongue, or throat
 - Trouble breathing

The most common side effect of NURTEC ODT in acute treatment of migraine attacks with or without aura is:

- nausea

The most common side effects of NURTEC ODT in preventive treatment of episodic migraine are:

- nausea
- stomach pain
- indigestion

These are not the only possible side effects of NURTEC ODT.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NURTEC ODT?

- Store NURTEC ODT in the blister package that it comes in.
- Store NURTEC ODT at room temperature between 68°F to 77°F (20°C to 25°C).

Keep NURTEC ODT and all medicines out of the reach of children.

General information about the safe and effective use of NURTEC ODT:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NURTEC ODT for a condition for which it was not prescribed. Do not give NURTEC ODT to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about NURTEC ODT that is written for health professionals.

What are the ingredients in NURTEC ODT?

Active ingredient in NURTEC ODT: rimegepant

Inactive ingredients in NURTEC ODT: benzyl alcohol, eucalyptol, gelatin, limonene, mannitol, menthol, menthone, menthyl acetate, sucralose, and vanillin

Manufactured for:

Biohaven Pharmaceuticals, Inc.

New Haven, CT 06510 USA

NURTEC and NURTEC ODT are registered trademarks of Biohaven Pharmaceutical Ireland DAC. Biohaven is a trademark of Biohaven Pharmaceutical Holding Company Ltd. For more information, go to www.nurtec.com or call 1-833-4NURTEC.

This Patient Information has been approved by the U.S. Food and Drug Administration
Revised: 12/2021

NURTEC CARTON



NURTEC ODT

rimegepant sulfate tablet, orally disintegrating

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72618-3000
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIMEGEPANT SULFATE (UNII: 1383NM3Q0H) (RIMEGEPANT - UNII:997WV895X)	RIMEGEPANT	75 mg in 75 mg

Inactive Ingredients

Ingredient Name	Strength
SUCRALOSE (UNII: 96K6UQ3ZD4)	
EUCALYPTOL (UNII: RV6J6604TK)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
LIMONENE, (+)- (UNII: GFD7C86Q1W)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
MENTHYL ACETATE, (+/-)- (UNII: LF3LEI45OH)	
VANILLIN (UNII: CHI530446X)	
MENTHOL, UNSPECIFIED FORM (UNII: L7T10EIP3A)	
MENTHONE, (+)- (UNII: 15F1B5K9A5)	
MANNITOL (UNII: 3OWL53L36A)	

Product Characteristics

Color	white (white to off-white)	Score	no score
Shape	ROUND	Size	14mm
Flavor	MINT	Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72618-3000-2	1 in 1 CARTON	03/05/2020	
1		75 mg in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212728	03/05/2020	

