PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]NURTEC® ODT

Rimegepant Orally Disintegrating Tablets

Tablets, 75 mg rimegepant (as rimegepant sulfate), Oral

Calcitonin-gene related peptide (CGRP) antagonist

Pfizer Canada ULC

17300 Trans-Canada Highway

Kirkland, Quebec H9J 2M5

Date of Initial Authorization:
DEC 1, 2023

Submission Control Number: 268384

RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NURTEC ODT (rimegepant orally disintegrating tablets) is indicated for:

- Acute treatment of migraine with or without aura in adults

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical trials with rimegepant did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects.

2 CONTRAINDICATIONS

NURTEC ODT is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hypersensitivity reactions, including dyspnea and rash, have occurred in less than 1% of patients treated with NURTEC ODT in clinical studies. Hypersensitivity reactions, including serious hypersensitivity, can occur days after administration. If a hypersensitivity reaction occurs, discontinue NURTEC ODT immediately and initiate appropriate therapy (see **2 CONTRAINDICATIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Hepatic impairment:
  The use of NURTEC ODT in patients with severe hepatic impairment should be avoided (see **10.3 Pharmacokinetics**).

- Renal impairment:
  Use of NURTEC ODT in patients with end-stage renal disease (CLcr < 15 mL/min) and those undergoing dialysis should be avoided (see **10.3 Pharmacokinetics**).

4.2 Recommended Dose and Dosage Adjustment

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

The maximum dose per day is 75 mg rimegepant. The safety of taking more than 15 doses in a 30-day period has not been established.

Geriatric population:

There is limited experience with rimegepant in patients aged 65 years or older. Clinical trials with rimegepant did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (n=131 treated with rimegepant). In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects. (see **7.1.4 Geriatrics**, **10.3 Pharmacokinetics**).

Hepatic impairment:

No dosage adjustment 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 **7.1.5 Hepatic Impairment**, **10.3 Pharmacokinetics**).

Renal impairment:

No dosage adjustment is required in patients with mild, moderate, or severe renal impairment. NURTEC ODT has not been studied, and therefore should be avoided, in patients with end-stage renal disease (CLcr < 15 mL/min) and in patients on dialysis (see **7.1.6 Renal Impairment**, **10.3 Pharmacokinetics**).

4.4 Administration

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. NURTEC ODT may be taken with or without food.
- Take the ODT immediately after opening the blister pack. Do not store the ODT outside the blister pack for future use.

5 OVERDOSAGE

There is limited clinical experience with NURTEC ODT overdosage. No specific antidote for the treatment of rimegepant overdose is available.

No overdose symptoms have been reported.

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. Rimegepant is unlikely to be significantly removed by dialysis because of high serum protein binding.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Orally disintegrating tablet / 75 mg Rimegepant (as rimegepant sulfate)	Benzyl alcohol, eucalyptol, gelatin, limonene, maize maltodextrin, mannitol, menthol, menthone, menthyl acetate, sucralose, and vanillin.

NURTEC ODT tablets are white to off-white, circular, debossed with the symbol .

NURTEC ODT is supplied in a carton, in the following 3 pack sizes:

- blister pack of 2 orally disintegrating tablets (ODTs), in a carton
- blister pack of 8 ODTs, in a carton
- 2 blister packs of 8 ODTs (16 ODTs in total), in a carton.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS**.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate human data on the developmental risk associated with the use of rimegepant in pregnancy. Animal studies demonstrate that at clinically relevant exposures rimegepant does not result in embryo-fetal death or fetal malformations. There were no developmental effects in rats at doses up to 60 mg/kg/day (exposures 46 times the human AUC at the maximum recommended human dose [MRHD] of 75 mg/day) or in rabbits at up to the highest dose tested of 50 mg/kg/day (exposures 10 times the MRHD of 75 mg/day). Please see **16 NON-CLINICAL TOXICOLOGY**. NURTEC ODT should not be used in pregnant women unless the expected benefit to the mother outweighs the potential risk to the fetus.

7.1.2 Breast-feeding

A lactation study was conducted in 12 healthy adult lactating women (26-37 years of age) who were between 2 weeks and 6 months post-partum and were administered a single oral dose of rimegepant 75 mg. The results have established an average milk-to-plasma ratio of 0.20 and a relative infant dose of less than 1% of the maternal weight-adjusted dose. There are no data on the effects of rimegepant on a breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for rimegepant and any potential adverse effects on the breastfed infant from rimegepant or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical trials with rimegepant did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (131 treated with rimegepant). In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects (see **4.2 Recommended Dose and Dosage Adjustment**).

7.1.5 Hepatic Impairment

Plasma concentrations of rimegepant were significantly higher in subjects with severe (Child-Pugh C) hepatic impairment (see **4.2 Recommended Dose and Dosage Adjustment, 10.3 Pharmacokinetics**). The use of NURTEC ODT in patients with severe hepatic impairment should be avoided.

7.1.6 Renal Impairment

Rimegepant has not been studied in patients with end-stage renal disease (CLcr < 15 mL/min) and in patients on dialysis and should be avoided in these patients (see **4.2 Recommended Dose and Dosage Adjustment, 10.3 Pharmacokinetics**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 1771 patients with migraine have been treated with NURTEC ODT or a bioequivalent oral dosage form in the acute treatment of migraine placebo-controlled registration studies. In the overall acute treatment development program, more than 954 patients were exposed for at least 12 months. Most of the adverse reactions reported were mild or moderate in severity.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Acute Treatment of Migraine

The safety of NURTEC ODT for the acute treatment of migraine in adults has been evaluated in 3 randomized, double-blind, placebo-controlled trials in 1771 patients with migraine who received one 75 mg dose of NURTEC ODT or a bioequivalent tablet formulation (see **14.1 Trial Design and Study Demographics per Indication**, Acute Treatment of Migraine). The most common adverse reaction was nausea. Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT.

Adverse reactions are listed by MedDRA system organ class in **Table 2**.

Table 2 – List of adverse reactions with acute treatment				
	NURTEC ODT n = [#] (%)	**Placebo ODT n = [#] (%)**	**Rimegepant Tablet* n = [#] (%)**	**Placebo Tablet* n = [#] (%)**
Gastrointestinal disorders: nausea	11/682 (1.6%)	3/693 (0.4%)	15/1089 (1.4%)	11/1089 (1.0%)

* Data for tablet formulation pooled from Studies 2 and 3.

Long-term safety

Long-term safety of rimegepant was assessed in a one-year, open-label study, during which 1197 patients received an average of 6.5 rimegepant tablets per 4 weeks for at least 6 months and 954 received an average of 6.6 rimegepant tablets per 4 weeks for at least 12 months. Approximately 2.6% of subjects experienced a serious adverse event and 2.7% of patients were withdrawn from NURTEC ODT because of an adverse reaction. The most common adverse reaction resulting in discontinuation in the long-term safety study was dizziness. The overall safety profile in the open-label, long-term safety study was consistent with that of the placebo-controlled studies (Study 1, 2, and 3).

8.3 Less Common Clinical Trial Adverse Reactions

Hypersensitivity reactions

Hypersensitivity, including dyspnea 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No adverse signals of concern were observed on any of the clinical laboratory assessments in the clinical program for NURTEC ODT.

8.5 Post-Market Adverse Reactions

No new adverse reactions have been identified based on cumulative international post-marketing experience and ongoing Phase 4 clinical trials.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In Vitro studies

- Enzymes

Rimegepant is a substrate of CYP3A4 and CYP2C9 (see **9.4 Drug-Drug Interactions**). 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

In vitro, rimegepant is a substrate of BCRP and P-gp efflux transporters. Inhibitors of P-gp and BCRP efflux transporters increase plasma concentrations of rimegepant. Rimegepant may be co-administered with BCRP transporter inhibitors and with weak to moderate P-gp only inhibitors. Strong P-gp inhibitors

may be co-administered no more frequently than once every 48 hours, based on a clinical interaction study with a potent dual P-gp and BCRP inhibitor (cyclosporine) and with a selective P-gp inhibitor (quinidine) resulted in significant increases 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 **9.4 Drug-Drug 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. No clinical drug interactions are expected for NURTEC ODT with these transporters at clinically relevant concentrations (see **9.4 Drug-Drug Interactions**).

9.3 Drug-Behavioural Interactions

The effect of rimegepant on sexual activity, driving, and operating machinery has not been studied. The interaction of rimegepant with cigarette smoking, cannabis use, and/or alcohol consumption has not been studied.

9.4 Drug-Drug Interactions

Table 3 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
CYP3A4 Inhibitors (e.g., clarithromycin, itraconazole, ritonavir, diltiazem, erythromycin, fluconazole, grapefruit juice)	*In vivo*	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). The concomitant administration of rimegepant with a moderate inhibitor of CYP3A4 (e.g., fluconazole), at steady state, increased rimegepant exposures (AUC) by 1.8-fold. 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. Concomitant administration of rimegepant with a weak inhibitor of CYP3A4 is not anticipated to have a clinically significant impact on rimegepant exposures.	Concomitant administration of NURTEC ODT with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ritonavir) **should be avoided** . Exercise caution during concomitant administration of rimegepant with moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, fluconazole). Another dose of NURTEC ODT within 48 hours **should be avoided** when it is concomitantly administered with moderate inhibitors of CYP3A4 (e.g., fluconazole).

Table 3 - Established or Potential Drug-Drug Interactions

CYP3A4 Inducers (e.g., phenobarbital, rifampicin, St John's wort (*Hypericum perforatum*), bosentan, efavirenz, modafinil)	*In vivo*	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 can lead to loss of efficacy. The effects of moderate or weak inducers of CYP3A4 on the pharmacokinetics of rimegepant are unknown. However, since rimegepant is a substrate for CYP3A4, drugs that are moderate inducers of CYP3A4 can also cause significant reduction in rimegepant exposure resulting in loss of efficacy. Clinically significant interaction is not anticipated with concomitant administration of weak inducers of CYP3A4 and 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**. The effect of CYP3A4 induction may last for up to 2 weeks after discontinuation of the strong or moderate CYP3A4 inducer.
BCRP and/or P-gp only Inhibitors (e.g., cyclosporine, verapamil, quinidine).	*In vivo*	Concomitant administration of 75 mg rimegepant (single dose) with a single 200 mg dose of cyclosporine, a strong inhibitor of the P-gp and BCRP transporters, resulted in 1.6-fold and 1.4-fold increase in rimegepant AUC and C_{max}, respectively. Upon concomitant administration of a single 75 mg dose of rimegepant and a single 600 mg dose of quinidine, a strong inhibitor of P-gp only, rimegepant AUC and C_{max} increased by approximately 1.6 fold and 1.7 fold, respectively. Based on the totality of the results, BCRP inhibition is not anticipated to significantly affect rimegepant exposures.	**Avoid** a second dose of NURTEC ODT within 48 hours after concomitant administration of the first dose with strong inhibitors of P-gp (e.g., cyclosporine, verapamil, quinidine).

Other drugs

CYP2C9 inhibitors:

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. In a drug-drug interaction study in healthy adult subjects, administration of a single 75 mg dose of rimegepant concurrent with steady state fluconazole (400 mg QD) increased AUC of rimegepant by approximately 1.8-fold while its C_{max} did not change significantly.

MATE1 substrates:

In a dedicated drug interaction study in healthy nondiabetic adult subjects, steady state administration of rimegepant 75 mg with metformin 500 mg, a MATE1 transporter substrate, at steady state, resulted in no clinically significant impact on either metformin pharmacokinetics or on glucose utilization.

CYP3A4 substrates and pharmacodynamic interactions:

In dedicated drug interaction studies in healthy adult subjects, rimegepant did not have a clinically significant effect on the pharmacokinetics of oral contraceptives (norelgestromin, ethinyl estradiol or midazolam (a sensitive CYP3A4 substrate) (see **10.2 Pharmacodynamics**).

In another drug interaction study in healthy adult subjects, steady state administration of oral rimegepant 75 mg did not affect sumatriptan (OCT1 substrate) pharmacokinetics (2 x 6 mg administered subcutaneously within one hour). Also, single-dose administration of sumatriptan did not have any meaningful effect on rimegepant pharmacokinetics.

Other calcitonin gene-related peptide (CGRP) Receptor Antagonists:

In a clinical study of two other CGRP receptor antagonists, a significant increase in cases of constipation was reported when these CGRP receptor antagonists were co-administered. Concomitant use of rimegepant with other CGRP receptor antagonists is not recommended.

9.5 Drug-Food Interactions

Following administration of NURTEC ODT under fed conditions T_{max} was delayed by approximately 1 to 1.5 hours. Consumption of a high-fat meal 30 minutes before administration of NURTEC ODT under or on top of the tongue decreased rimegepant AUC_T by 32% and 38%, and C_{max} by 42% and 53%, respectively. Similarly, consumption of a low-fat meal 30 min before administration of NURTEC ODT under the tongue decreased rimegepant AUC_T and C_{max} by approximately 28% and 36%, respectively, compared with administration under fasting conditions.

NURTEC ODT was administered without regard to food in clinical safety and efficacy studies. It is not known whether there is any impact on efficacy when there is a reduction in rimegepant exposure when administered with food.

9.6 Drug-Herb Interactions

See **9.4 Drug-Drug Interactions** regarding concomitant use with St. John's wort (a CYP3A4 inducer).

9.7 Drug-Laboratory Test Interactions

Interactions of NURTEC ODT with laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Rimegepant is a calcitonin gene-related peptide receptor antagonist. 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.

10.2 Pharmacodynamics

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.

Abuse liability has not been studied in humans or in animals.

Cardiac Electrophysiology

In a double-blind, randomized, placebo- and positive-controlled, crossover ECG assessment study in healthy subjects (N=38), single 75 mg and 300 mg doses of rimegepant did not show any pharmacodynamic effect on the QTc interval.

10.3 Pharmacokinetics

CYP2C9 polymorphism

Rimegepant C_{max} and $AUC_{0\text{-}inf}$ 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, n=2). Since the contribution of CYP2C9 to rimegepant metabolism is considered minor, CYP2C9 polymorphism is not expected to significantly affect its exposure.

Absorption

Following oral administration of NURTEC ODT, rimegepant is absorbed with the maximum concentration at 1.5 to 2.0 hours. The absolute oral bioavailability of rimegepant is approximately 64%.

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 the primary form (~77%) with no major metabolites (i.e., > 10%) detected in plasma.

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%).

Special Populations and Conditions

- **Geriatrics:** In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly (≥ 65 years) and younger (18-45 years) subjects.
- **Sex**: No clinically significant differences in the pharmacokinetics of rimegepant were observed based on sex.
- **Genetic Polymorphism**: No clinically significant differences in the pharmacokinetics of rimegepant were observed based on CYP2C9 genotype.
- **Ethnic Origin**: No clinically significant differences were observed in studies where the pharmacokinetics of rimegepant in White, Black, and Japanese study participants were assessed.
- **Hepatic Insufficiency**: 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 **4.2 Recommended Dose and Dosage Adjustment**, *Hepatic impairment*).
- **Renal Insufficiency**: 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 matched control), total rimegepant exposure was increased by 6%, 40%, and 4%, respectively following a single 75 mg dose. NURTEC ODT has not been studied in patients with end-stage renal disease (CLcr < 15 mL/min) and in patients undergoing dialysis (see **4.2 Recommended Dose and Dosage Adjustment**, *Renal impairment*).
- **Obesity**: No clinically significant differences in the pharmacokinetics of rimegepant were observed based on body weight.

11 STORAGE, STABILITY AND DISPOSAL

Store NURTEC ODT at room temperature (15°C to 30°C).

12 SPECIAL HANDLING INSTRUCTIONS

Instructions for handling the medicinal product before administration are:

- Use dry hands when opening the blister pack.
- Peel back the foil covering of one blister and gently remove the orally disintegrating tablet. Do not push the tablet through the foil.
- Take the tablet immediately after opening the blister pack. Do not store the tablet outside the blister pack for future use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name: Rimegepant (as rimegepant sulfate)

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-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidine-1-carboxylate hemisulfate sesquihydrate

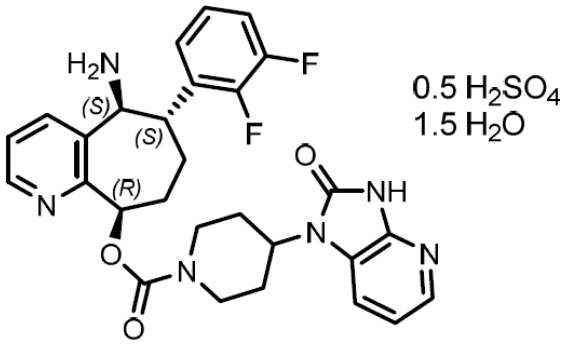
Molecular formula $C_{28}H_{28}F_2N_6O_3 \bullet 0.5H_2SO_4 \bullet 1.5H_2O$

$C_{28}H_{28}F_2N_6O_3$ (free base)

Molecular mass:

- Hemisulfate sesquihydrate: 610.63 Daltons
- Free base: 534.57 Daltons

Structural formula:



Physicochemical properties: Rimegepant hemisulfate sesquihydrate is a white to off-white powder, that is highly soluble at pH below 5.6, and slightly hygroscopic.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Acute Treatment of Migraine, With or Without Aura

The efficacy of rimegepant for the acute treatment of migraine with or without aura in adults was studied in three randomized, double-blind, placebo-controlled single migraine attack trials. Study 1 was conducted using the NURTEC ODT formulation, while Study 2 and Study 3 used a bioequivalent immediate release tablet. These studies included patients with a history of migraine with or without aura, as defined by the ICHD-3 beta diagnostic criteria, who experienced 2-8 migraine attacks per month with moderate to severe headache pain.

Table 5 - Summary of patient demographics for clinical trials in acute treatment of migraine (modified intent-to-treat population, mITT^)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1 (NCT03461757)	Randomized, double-blind, placebo-controlled	Rimegepant, 75 mg, Oral (ODT), single dose	N=669, Rimegepant; N=682, placebo	40.2 years (18.1-75.7)	15.1% male 84.9% female
Study 2 (NCT03235479)	Randomized, double-blind, placebo-controlled	Rimegepant, 75 mg, Oral (tablet), single dose	N=543, Rimegepant; N=541, placebo	41.6 years (18.6-73.3)	14.5% male 85.5% female
Study 3 (NCT03237845)	Randomized, double-blind, placebo-controlled	Rimegepant, 75 mg, Oral (tablet), single dose	N=537, Rimegepant; N=535, placebo	40.6 years (18.1-83.6)	11.3% male 88.7% female

^ The mITT population were randomized subjects who were randomized only once, took study medication, had a baseline migraine of moderate to severe pain intensity and who provided at least 1 postbaseline efficacy data point

Across the 3 pivotal placebo-controlled trials, approximately 76.0% of patients were White, 19.6% were Black, and 4.4% were Other, including Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or multiple races. The three studies randomized patients to NURTEC ODT 75 mg or rimegepant tablet or matching placebo. Patients were instructed to treat a migraine of moderate to severe headache pain intensity at the time of headache onset. 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 15.4% of patients were taking preventive medications for migraine at baseline. Across the 3 pivotal trials, the most commonly used preventive medications were topiramate, amitriptyline, propranolol, and nortriptyline, and none of the patients in the three studies were on concomitant preventive medication that act on the calcitonin gene-related peptide pathway (CGRP receptor antagonists).

The co-primary endpoints were the percentage of patients reporting:

- No pain at 2 hours post-dose
- Absence of their most bothersome symptom (MBS) at 2 hours post-dose

Patients were instructed to select an MBS other than headache pain (i.e., photophobia, phonophobia, or nausea) at the onset of the migraine and before taking study medication. Across the 3 pivotal studies, of those who selected an MBS, photophobia was selected by 55.0%, nausea by 29.9%, and phonophobia by 15.1%.

Table 6 Migraine Efficacy Endpoints for Acute Treatment Studies (mITT)

	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

In all three studies, the results of efficacy endpoints of interest such as use of rescue medication within 24 hours post-dose, supported the results of the primary endpoints (Table 6). For example, in Study 1, 34.9% of rimegepant-treated patients reported freedom from photophobia at 2 hours post-dose, versus 24.8% of placebo-treated patients.

14.2 Comparative Bioavailability Studies

An open-label, randomized, two-treatment, two-period, two-sequence, crossover, single-dose (1 × 75 mg), oral comparative bioavailability study of NURTEC ODT (rimegepant, as rimegepant sulfate) 75 mg orally disintegrating tablets administered under or on top of the tongue was conducted in 24 healthy, adult, male and female subjects under fasting conditions. Comparative bioavailability data from 24 subjects that were included in the statistical analysis are presented in the following table:

Table 7: Summary of Comparative Bioavailability Data

Rimegepant (1 x 75 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	4896.85 5033.40 (23.48)	4748.71 4914.43 (25.23)	103.0	96.0 – 111.0
AUC_I (ng·h/mL)	4910.09 5046.02 (23.40)	4762.64 4927.57 (25.15)	103.0	96.0 – 111.0
C_{max} (ng/mL)	902.21 958.83 (36.75)	823.75 861.29 (31.21)	110.0	94.0 – 127.0
T_{max}[3] (h)	1.50 (0.83 – 2.54)	1.99 (0.50 – 2.50)		
$T_{1/2}$[4] (h)	8.12 (21.30)	8.18 (19.90)		

[1] NURTEC® ODT (rimegepant, as rimegepant sulfate) orally disintegrating tablets administered under the tongue, 75 mg
[2] NURTEC® ODT (rimegepant, as rimegepant sulfate) orally disintegrating tablets administered on top of the tongue, 75 mg
[3] Expressed as median (range) only
[4] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: 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.

Carcinogenicity: Oral administration of rimegepant to Tg.rasH2 mice sensitive to both genotoxic and non-genotoxic human carcinogens for 26 weeks, and to rats for 91-100 weeks, resulted in no evidence

of drug-induced tumors in either species. In these animal studies, the plasma exposure (AUC) at the highest dose tested was approximately 350 times (mice) and 30 times (rats) of that in humans at the maximum recommended human dose (MRHD) of 75 mg/day.

Genotoxicity and Mutagenesis: Rimegepant was negative in *in vitro* and *in vivo* assays.

Reproductive and Developmental Toxicology: Animal studies showed no clinically relevant impact on female and male fertility. Oral administration of rimegepant to male and female rats prior to and during mating, and continuing in females to gestation day 7, resulted in reduced fertility at the highest dose (150 mg/kg/day) tested.

The no-effect dose for impairment of fertility and early embryonic development in rats of 60 mg/kg/day was associated with plasma drug exposures (AUC) approximately 30 times the MRHD of 75 mg/day.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]NURTEC® ODT

Rimegepant Orally Disintegrating Tablets

Read this carefully before you start taking **NURTEC ODT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NURTEC ODT**.

Serious Warnings and Precautions

- If an allergic reaction occurs, stop taking NURTEC ODT and contact your healthcare professional right away. Severe allergic reactions, including shortness of breath and rash, can occur days after administration.

What is NURTEC ODT used for?

NURTEC ODT is used in adults to treat an active migraine attack.

How does NURTEC ODT work?

NURTEC ODT contains the active ingredient rimegepant hemisulfate sesquihydrate and belongs to a group of medicines known as "calcitonin gene-related peptide (CGRP) antagonists". It reduces the activity of a substance in the body called calcitonin gene-related peptide (CGRP) that causes migraine attacks.

What are the ingredients in NURTEC ODT?

Medicinal ingredient: rimegepant hemisulfate sesquihydrate.

Non-medicinal ingredients: Benzyl alcohol, eucalyptol, gelatin, limonene, maize maltodextrin, mannitol, menthol, menthone, menthyl acetate, sucralose, and vanillin.

NURTEC ODT comes in the following dosage forms:

Orally Disintegrating Tablets (ODTs): 75 mg of rimegepant (as rimegepant sulfate).

Do not use NURTEC ODT if:

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NURTEC ODT. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- have kidney problems.
- are pregnant, think you may be pregnant or are planning to have a baby. Talk to your healthcare professional before using NURTEC ODT. Your healthcare professional will decide if NURTEC ODT is right for you.
- are breast-feeding or are planning to breast-feed. Talk to your healthcare professional before using NURTEC ODT. You and your healthcare professional will decide if you will use NURTEC ODT while breast-feeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

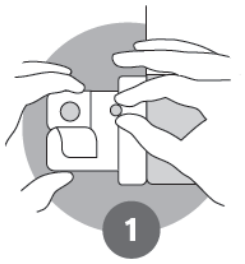
The following may interact with NURTEC ODT:

- itraconazole and clarithromycin (medicines used to treat fungal or bacterial infections).
- ritonavir and efavirenz (medicines to treat HIV infections).
- bosentan (a medicine used to treat high blood pressure).
- St. John's wort (a herbal remedy used to treat depression).
- phenobarbital (a medicine used to treat epilepsy).
- rifampicin (a medicine used to treat tuberculosis).
- modafinil (a medicine used to treat narcolepsy).
- fluconazole and erythromycin (medicines used to treat fungal or bacterial infections).
- diltiazem, quinidine, and verapamil (medicines used to treat an abnormal heart rhythm, chest pain (angina) or high blood pressure).
- cyclosporine (a medicine used to prevent organ rejection after an organ transplant).
- grapefruit juice.
- calcitonin gene-related peptide (CGRP) antagonists (medicines used to treat migraines).

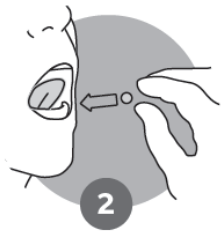
How to take NURTEC ODT:

- NURTEC ODT is for oral use.
- NURTEC ODT may be taken with or without food.
- Take NURTEC ODT immediately after opening the blister pack. Do **not** store the tablets outside the blister pack for future use.

Instructions for Use of NURTEC ODT:



1. Using dry hands, peel back the foil covering of one blister pack and gently remove the tablet. Do **not** push the tablet through the foil.



2. As soon as the blister pack is opened, remove the tablet and place it on or under the tongue, where it will dissolve. It can then be swallowed without any additional liquid.

Usual dose:

Your healthcare professional will tell you the right dose of NURTEC ODT for you. This will depend on if you take certain medicines such as fluconazole, erythromycin, diltiazem, quinidine, verapamil, and cyclosporine.

The recommended dose is one tablet of NURTEC ODT (75 mg) once a day, as needed.

Do **not** take more than the maximum dose of 75 mg per day.

Overdose

If you think you, or a person you are caring for, have taken too much NURTEC ODT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using NURTEC ODT?

These are not all the possible side effects you may have when taking NURTEC ODT. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of NURTEC ODT may include:

- nausea.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic reaction: shortness of breath, rash, difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick, vomiting, hives, or swelling of the face, lips, tongue or throat.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.htm) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store NURTEC ODT in the blister pack that it comes in at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about NURTEC ODT:

- Talk to your healthcare professional;
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.pfizer.ca), or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

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