# Taiwan Food and Drug Administration

# Assessment Report

**Trade Name：紐舒泰口溶錠 75 毫克 / Nurtec ODT 75 mg**

**Active Ingredient：Rimegepant sulfate**

**License Number： MOHW-PI 028633**

**Applicant：輝瑞大藥廠股份有限公司**

**Approval Date：113/1/5**

**Indication：**
偏頭痛的急性治療
適用於成人有或無預兆之偏頭痛的急性治療

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

# 1. Background Information

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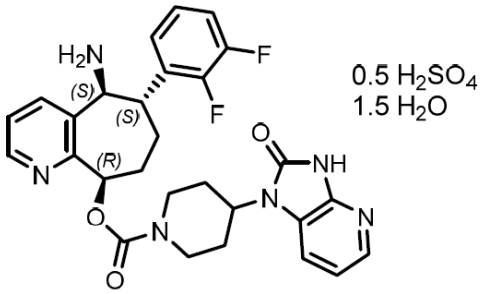
|---|---|
| **Trade Name** | 紐舒泰口溶錠 75 毫克 / Nurtec ODT 75 mg |
| **Active Ingredient(s)** | Rimegepant sulfate |
| **Applicant** | 輝瑞大藥廠股份有限公司 |
| **Dosage Form & Strengths** | 口溶錠 75 mg |
| **Indication** | 偏頭痛的急性治療<br>適用於成人有或無預兆之偏頭痛的急性治療<br>Acute Treatment of Migraine<br>NURTEC ODT is indicated for the acute treatment of migraine with or without aura in adults. |
| **Posology** | 建議劑量為需要時每天一次 75 毫克 rimegepant。 |
| **Pharmacological Category**<br>**ATC Code** | N02CD06 |

# 2. Summary Report

### 2.1 Chemistry, Manufacturing and Controls Evaluation

#### 2.1.1 Drug substance

The drug substance, rimegepant sulfate, is chemically designated as (5*S*,6*S*,9*R*)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidine-1- carboxylate hemisulfate sesquihydrate and has the following structure:




It is a white to off-white powder. The molecular formula and the molecular weight are $C_{28}H_{28}F_2N_6O_3 \cdot 0.5\ H_2SO_4 \cdot 1.5\ H_2O$ and 610.63 Daltons, respectively.

Adequate information of characterization of the drug substance has been provided. The structure of rimegepant sulfate is confirmed by $^{1}$H-NMR spectroscopy, $^{13}$C-NMR spectroscopy, infrared spectroscopy, UV-visible absorption, mass spectrometry and single crystal X-ray

crystallography. The specification for the drug substance includes tests for appearance, identification, related substances, residual solvents, sulfate content, residue on ignition, water content, particle size, crystalline form, microbial limits, specified pathogens and assay. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

### 2.1.2 Drug product

Rimegepant sulfate orally disintegrating tablets are for oral administration and each orally disintegrating tablet contains 75 mg of rimegepant free base. The excipients used in the drug product comply with compendial monographs or in-house.

The specification for the drug product includes appearance, identification, assay, related substances, water content, disintegration, dissolution, uniformity of dosage units, microbial limits and specified pathogens. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 48 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of drug product can be granted for 48 months under the storage condition of 30°C.

## 2.2 Preclinical Pharmacology/Toxicology Evaluation

The primary pharmacology studies demonstrated that rimegepant is an antagonist of the human CGRP receptor. In vitro, rimegepant is a competitive antagonist of the human CGRP receptor, which displayed concentration-dependent inhibition of radiolabeled-CGRP binding to the human CGRP receptor of a neuronal cell line with a picomolar binding affinity (Ki). Functionally, rimegepant showed concentration-dependent inhibition of CGRP-stimulated cAMP production with an IC50 in the picomolar range in a cellular assay using neuronal cells.

Rimegepant showed comparable cross-reactivity to human and non-human primate CGRP receptors but was much less active (~1,300 to 6,300 folds) on those non-primate CGRP receptors tested. Regarding receptor selectivity, rimegepant displayed up to > 100,000-fold selectivity for CGRP over other members of the calcitonin family. In vivo, rimegepant demonstrated dose-dependent inhibition of CGRP-induced increases in facial blood flow in the marmoset assay, in which a strong agonist challenge was specifically designed to mimic CGRP release during severe migraine. The effect of rimegepant persisted for at least 1.75 hours, the latest time point in the marmoset assay. Ex vivo, rimegepant did not induce contraction of the human coronary artery or intracranial artery at concentrations up to 10 μM and 3 μM,

respectively.

In vitro, rimegepant showed no clinically meaningful off-target interactions in a panel of receptors/transporters/channels/enzymes. Safety pharmacology studies conducted in vitro and in rats and monkeys showed no remarkable rimegepant-related effects on safety pharmacology endpoints.

Oral single dosing in rats up to 300 mg/kg was well tolerated. In monkeys, single oral dosing up to 300 mg/kg revealed only transient clinical signs. In the repeated-dose toxicity studies, the primary findings at higher doses of rimegepant included hepatic lipidosis in rodent (a rodent-specific effect), generally minimal to mild intravascular hemolysis in rats and monkeys, and sporadic emesis in monkeys. Evidence of intravascular hemolysis was observed at generally higher doses in rats and monkeys, providing systemic exposures ≥ 95-fold and ≥ 9-fold the human AUC at 75 mg/day, respectively. Rimegepant-related emesis observed in monkeys' pivotal studies up to 3 months occurred at doses providing systemic exposures ≥ 37-fold the human AUC at 75 mg/day.

Rimegepant was negative for genotoxicity, carcinogenicity, and phototoxicity.

Rimegepant had no effects on male or female fertility or early embryonic development in rats at doses providing safety margins of ≥ 29-fold and ≥ 46-fold for males and females, respectively. Rimegepant was not teratogenic in rats and rabbits. However, fetal toxicity had been observed at the high dose which was associated with maternal toxicity in the rats. Rimegepant showed no toxicity on embryofetal development at doses providing safety margins of approximately up to 46-fold and 10-fold in rats and rabbits, respectively. Rimegepant had no effect on pre- and postnatal development in rats at doses providing a safety margin of up to 38-fold. Lastly, rimegepant showed no effect on the growth, development, or reproductive performance of juvenile rats at doses providing a safety margin of up to 21-fold.

**2.3 Clinical Pharmacology Evaluation**

**2.3.1 General Pharmacodynamics and Pharmacokinetics**

The oral bioavailability of rimegepant was estimated to be 64% and $T_{max}$ was reached 1.5 hours after dosing. Absorption of Nurtec ODT administered sublingually and on top of tongue were very similar. Rimegepant 75 mg has low to moderate PK variability. 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%. It was recommended to be taken with or without food.

Rimegepant exhibits greater than dose proportional increases in exposure following single oral administration over the dose range of 10 mg to 150 mg. The steady state volume of distribution of rimegepant is 120 L. Plasma protein binding of rimegepant is approximately 96%. Rimegepant is primarily circulated in unchanged form (~77% of the dose) with no major metabolites (i.e., > 10%) detected in plasma. A portion of rimegepant would be metabolized via CYP3A4 and to a lesser extent, CYP2C9 to a series of minor metabolites, none of which contribute pharmacological activity. 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%).

**2.3.2 Interaction Studies**

Rimegepant is a substrate of CYP3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters. Concomitant administration of rimegepant with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in rimegepant exposure (AUC by 4-fold and $C_{max}$ 1.5-fold). Concomitant administration of rimegepant with strong CYP3A4 inhibitors is not recommended. Concomitant administration of rimegepant with fluconazole, a moderate CYP3A4 inhibitor, 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. Concomitant administration of rimegepant with rifampicin, a strong CYP3A4 inducer, resulted in a significant decrease (AUC reduced by 80% and $C_{max}$ by 64%) in rimegepant exposure. Concomitant administration of rimegepant with strong CYP3A4 inducers or moderate CYP3A4 inducers is not recommended.

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 (nearly 50%). BCRP inhibition is not anticipated to significantly affect rimegepant exposures. Another dose of rimegepant within 48 hours should be avoided when it is concomitantly administered with strong inhibitors of P-gp.

**2.3.3 Special Populations**

No clinically significant differences in the pharmacokinetics of rimegepant were observed based on age, sex, race/ethnicity, body weight, migraine status, or CYP2C9 genotype. The pharmacokinetics of rimegepant in subjects with mild, moderate, and severe renal impairment to that with normal subjects, a less than 50% increase in total rimegepant exposure was observed following a single 75 mg dose. No dose frequency adjustment is recommended for subjects with mild, moderate or severe renal impairment. Rimegepant has not been studied in patients with end stage renal disease (ESRD) and in patients on dialysis. The use of rimegepant

is not recommended in ESRD patients and in patients on dialysis.

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. No dose adjustment is required in patients with mild or moderate hepatic impairment. The use of rimegepant is not recommended in patients with severe impairment (Child-Pugh class C) since the exposure of rimegepant (unbound AUC) following a single 75 mg dose was 3.89-fold higher comparing to normal subjects.

**2.4 Clinical Efficacy and Safety Evaluation**

**2.4.1 Efficacy Results**

The Applicant provided 4 pivotal phase III acute treatment studies (Studies 301, 302, 303 and 310) in subjects with acute migraine to claim efficacy of rimegepant (Nurtec).

For acute treatment of migraine, when comparing efficacy of the co-primary endpoint, freedom from pain and freedom from MBS at 2-hour post-dose, with placebo arm, rates of condition improvement were observed in the 4 pivotal phase III studies (5%-14.7%; all p-values < 0.03). Subgroup, sensitivity and secondary efficacy analyses coincided with the main analysis result.

**2.4.2 Safety Results**

Main TEAEs include hypersensitivity, nausea, abdominal pain and dyspepsia.

**2.5 Bridging Study Evaluation**

No dedicated ethnic PK study was conducted in patient population to evaluate the ethnic effects on rimegepent. However, the PK data from healthy volunteers was similar in Chinese and western population. The ethnic difference was negligible from PK point of view.

The sponsor provided the results of Study BHV-3000-310 (conducted in China and South Korea) as bridging data of acute treatment of migraine. In this study, 1431 eligible subjects were randomized, of whom 1340 received treatment. Freedom from pain at 2 hours post-dose was 19.9% for rimegepant and 10.7% for placebo ($p<0.0001$ for difference of 2 groups); freedom from the MBS at 2 hours post-dose was 50.5% for rimegepant and 35.8% for placebo ($p<0.0001$ for difference of 2 groups). The safety profile is similar to global trials. The bridging study was waived for the indication of acute treatment of migraine.

For the indication of preventive treatment of migraine. There were few East Asian subjects in the only pivotal study 305. Therefore, bridging study was not waved for migraine prevention.

The sponsor should provide the results of on-going preventive studies in East Asians (Study 309 in Japan and Study 319 in China), or other sources, for BSE of preventive treatment indication.

**2.6 Conclusion**

The benefit/risk ratio of acute treatment of migraine is favorable, approval of Nurtec ODT for the indication of acute treatment of migraine in adult is recommended.

Approval of preventive treatment of episodic migraine is not recommended as the Bridging study has not been waved for preventive treatment of episodic migraine.
The sponsor plans to re-apply for the indication of preventive treatment of episodic migraine when additional clinical trial data in East Asian participants are available to support this indication.

## 3. Post-Marketing Requirements

Routine pharmacovigilance.