Taiwan Food and Drug Administration

Assessment Report

Trade Name：倍拉維 150 毫克/100 毫克膜衣錠 / Paxlovid 150 mg/100 mg Film-coated Tablets

Active Ingredient：nirmatrelvir / ritonavir

License Number：MOHW-PI-028474

Applicant：輝瑞大藥廠股份有限公司

Approval Date：2023/5/18

Indication：

適用於治療 12 歲以上、具有進展為重症風險因子之輕度至中度新型冠狀病毒疾病(COVID-19)病人。

Indicated for the treatment of adults and pediatric patients (12 years of age and older) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19.

Background Information

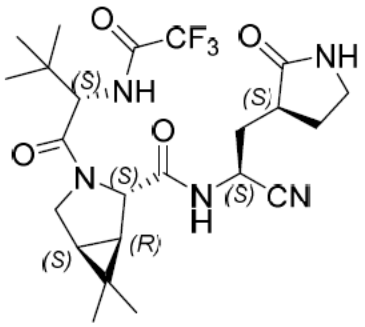
Trade Name	倍拉維 150 毫克/100 毫克膜衣錠 / Paxlovid 150 mg/100 mg Film-coated Tablets
Active Ingredient(s)	nirmatrelvir / ritonavir
Applicant	輝瑞大藥廠股份有限公司
Dosage Form & Strengths	膜衣錠 nirmatrelvir 150/ ritonavir 100mg
Indication	適用於治療 12 歲以上、具有進展為重症風險因子之輕度至中度新型冠狀病毒疾病(COVID-19)病人。
Posology	詳細內容請參閱仿單
Pharmacological Category **ATC Code**	J05AE30

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance - Nirmatrelvir

The drug substance, nirmatrelvir, is chemically designated as (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2- carboxamide and has the following structure:



It is a white to pale colored powder. The molecular formula and the molecular weight are $C_{23}H_{32}F_3N_5O_4$ and 499.54 Daltons, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of nirmatrelvir has been confirmed by elemental analysis, infrared spectrophotometry (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV spectrophotometry. Stereochemistry is determined by single crystal X-ray diffraction analysis.

Adequate specification has been presented for the drug substance. 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 - Nirmatrelvir Tablet

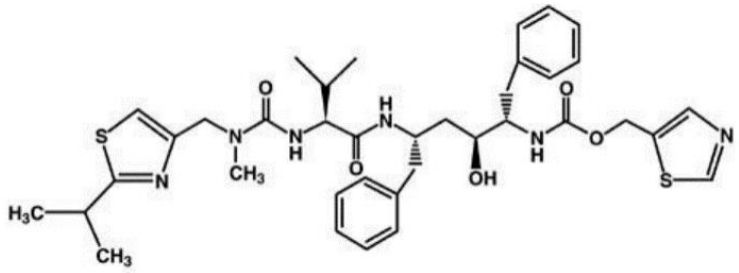
The drug product is a film-coated tablet. Each tablet contains 150 mg nirmatrelvir. The specifications for excipients used in the drug product formulation are adequate.

Adequate specification has been presented for the drug product. Analytical methods are described well and validated.

Stability studies of the drug product under long-term conditions (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.1.3 Drug Substance - Ritonavir

The drug substance, ritonavir, is chemically designated as 10-hydroxy -2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)] and has the following structure:



It is a white or almost white powder. The molecular formula and the molecular weight are $C_{37}H_{48}N_6O_5S_2$ and 720.95 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of ritonavir has been confirmed by infrared spectrophotometry (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV spectrophotometry.

Adequate specification has been presented for the drug substance.

2.1.4 Drug Product - Ritonavir Tablet

The drug product is a film-coated tablet. Each tablet contains 100 mg ritonavir. The specifications for excipients used in the drug product formulation are adequate.

Adequate specification has been presented for the drug product. Analytical methods are described well and validated.

Stability studies of the drug product under long-term conditions (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

Stability studies for the drug product in the co-packaged container under long-term conditions (25°C/60% RH and 30°C/75% RH) and accelerated conditions (40°C/75% RH) are also been carried out.

2.1.5 Paxlovid

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. Based on available stability data, the shelf-life of Paxlovid can be granted for 24 months under the storage condition of 25°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nsp5 protease. Inhibition of the SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors, which leads to the prevention of viral replication. Nirmatrelvir demonstrates broad-spectrum inhibitory activity against both alpha- and beta-coronavirus types but shows greater selectivity for the SARS-CoV-2 M^{pro}. In Vero E6 P-gp knockout cells or VeroE6 TMPRSS2 cells with a P-gp inhibitor, nirmatrelvir could inhibit the ancestral SARS-CoV-2 strain and several variants of concern, including Omicron BA.1 and BA.2. Substitutions at several amino acid positions in M^{pro} were found to reduce the potency of nirmatrelvir; however, the clinical significance of these substitutions is unknown.

In mouse models with mouse-adapted SARS-CoV-2 infection, oral administration of nirmatrelvir with ritonavir could reduce the lung viral titers and ameliorate lung histopathological changes. In safety pharmacology studies, nirmatrelvir caused movement changes, higher respiratory rate, and minute volume in rats at 17-fold higher exposures than in humans. Nirmatrelvir caused changes in cardiovascular parameters in monkeys at 3.6 times the human exposures, all of which resolved within 24 hours after the first dose. Ritonavir inhibits the CYP3A-mediated metabolism and increases the plasma concentrations of nirmatrelvir.

2.2.2 Toxicological Studies

The toxicity of nirmatrelvir was evaluated in GLP repeated-dose toxicity studies up to 1 month in duration in rats and cynomolgus monkeys. There were no adverse findings in any of the studies, and the NOAELs were the highest dose in each study, providing safety margins of 8.0 (rats) and 14.4 (monkeys). Nirmatrelvir and ritonavir showed no genotoxicity potential.

Carcinogenicity studies with nirmatrelivir were not conducted due to clinical use for only 5 days. Long-term studies of ritonavir have revealed a rodent-specific carcinogenic potential that was not thought to be relevant to humans.

No adverse effects of nirmatrelvir on fertility parameters and embryo-fetal development were observed in rats up to 1000 mg/kg/day. In the rabbit embryo-fetal development study, high dose of nirmatrelvir (1000 mg/kg/day) produced minor effects on maternal body weight gain and food consumption and caused lower fetal body weights. The rabbit embryo-fetal developmental NOAEL was 300 mg/kg/day, providing a safety margin of 2.8. In the rat pre- and postnatal development toxicity study, preweaning pup body weight gain decreased at 1000 mg/kg/day, but this effect was transient and did not impact F1 offspring body weight or reproductive performance. Additionally, Ritonavir did not affect fertility in rats, and developmental toxicity observed in rats and rabbits occurred mainly at maternally toxic dosages.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The absorption of nirmatrelvir/ritonavir in fasted state occurred with the median T_{max} ranging between 0.75 hours to 2.75 hours. Following single dose of nirmatrelvir at 250 and 750 mg oral suspension, enhanced with 100 mg ritonavir, the increase in exposure was less than dose proportional. Following repeat-dose of nirmatrelvir/ritonavir up to 500 mg/100 mg BID as oral suspension in the fasted state,, the increase in systemic exposure at steady state was less than dose proportional. Mean steady state was achieved on Day 2 with ~2-fold accumulation. Mean $t_{1/2}$ values ranged between approximately 6.8 hours to 8.0 hours.Dosing with a high fat meal increased nirmatrelvir C_{max} by 61% and AUC_{last} by 20% relative to fasting conditions following administration of 300 mg nirmatrelvir (2 ×150 mg) boosted with 3 doses of 100 mg ritonavir final commercial tablets.

Binding of nirmatrelvir to human plasma proteins was moderate (average f_u=0.31) and concentration-independent. *In vitro* studies indicated CYP3A4 was the major contributor to the oxidative metabolism of nirmatrelvir. Unchanged nirmatrelvir was the predominant drug-related entity in circulation in plasma from healthy adults administered with a single oral dose of 300 mg nirmatrelvir in the presence of ritonavir. The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact drug. A total of 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively.

2.3.2 Interaction Studies

The potential drug interactions for nirmatrelvir/ritonavir from a victim and perpetrator perspective were assessed in several *in vivo* drug-interaction studies. Co-administration of multiple oral doses of itraconazole 200 mg increased steady state nirmatrelvir AUC_{tau} and C_{max} by 39% and 19%, respectively. Co-administration of multiple oral doses of carbamazepine titrated up to 300 mg BID decreased single dose nirmatrelvir AUC_{inf} and C_{max} by 55% and 43%, respectively. The percent ratios of geometric means for dabigatran AUC_{inf} and C_{max} were 194% and 233% respectively, following dabigatran administration with multiple doses of nirmatrelvir/ritonavir compared to dabigatran alone. The percent ratios of the geometric means for midazolam AUC_{inf} and C_{max} were 1430% and 368%, respectively, when midazolam was co-administered with nirmatrelvir/ritonavir compared to midazolam administered alone.

2.3.3 Special Populations

The impacts of intrinsic and extrinsic factors were evaluated through a population PK analysis. In addition, two dedicated PK studies were performed in participants with hepatic impairment (Study C4671010) and renal impairment (Study C4671011) to provide reasonable dose recommendations.

In Study C4671011, mean AUC_{inf} in mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severely (eGFR <30 mL/min) renally impaired patients was higher than those in healthy participants by 24%, 87% and 204%, respectively. In Study C4671010, the exposure of nirmatrelvir in participants with moderate (Child-Pugh Class B) hepatic impairment was comparable to those in participants with normal hepatic function. Nirmatrelvir/ritonavir has not been studied in patients with severe (Child-Pugh Class C) hepatic impairment.

Based on a population PK model, the dosing regimen is expected to result in comparable steady-state plasma exposure of nirmatrelvir in patients 12 years of age and older and weighing at least 40 kg to those observed in adults after adjusting for body weight. Age and gender did not affect the PK of nirmatrelvir.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, a pivotal study ([C4671005]) was provided to support the efficacy of Paxlovid, indicated for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighting at least 40 kg) who are high risk for progression to severe COVID-19, including hospitalization or death.

Study C4671005 (high risk) was conducted in nonhospitalized, symptomatic adults with COVID-19 who had atleast 1 risk factor for progression to severe disease. Participants must

have had laboratory confirmed SARS-CoV-2 infection and symptom onset no more than 5 days before randomization, with at least one sign or symptom of COVID-19 on the day of randomization. Eligible participants received nirmatrelvir/ritonavir 300/100 mg or matched placebo (1:1 randomization) orally every 12 hours for 5 days (10 total doses).

In participants who were treated < 3 days after symptom onset and had not received or were not expected to receive mAb treatment (mITT) at baseline, Paxlovid significantly reduced the proportion of participants with COVID-19-related hospitalization or death through Day 28 (0.723% vs. 6.531%, $p < 0.0001$) compared to placebo.

The 1st key secondary efficacy endpoint was also met. That is, in participants who were treated < 5 days after symptom onset and had not received or were not expected to receive mAb treatment at baseline (mITT1), Paxlovid also significantly reduced the proportion of participants with COVID-19-related hospitalization or death through Day 28 (0.9% vs. 6.5%, $p < 0.0001$) compared to placebo. Furthermore, treatment with Paxlovid significantly shortened the time to sustained alleviation of all targeted COVID-19-related signs and symptoms ($p < 0.0001$).

Study C4671002 (standard-risk) enrolled adults who had no risk factors for progression to severe COVID-19 listed in Study C4671005, or who had risk factors but were fully vaccinated. However, Study C4671002 was early terminated due to a very low rate of hospitalization or death observed in the standard-risk patient population. The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met. In an exploratory analysis of the subgroup of fully vaccinated participants with at least 1 risk factor for progression to severe disease, a 58% relative risk reduction compared to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.
The result did not reach statistical significance

Study C4671005 was conducted during July to December, 2021. The dominant strain at that period was the SARS-CoV-2 Delta variant. Real-world evidence from the US after the emergence and global predominance of the Omicron variant was provided, indicated relative risk reductions ranging from approximately 50% to 80% against hospitalization or deaths.

As result, there is sufficient evidence to support the efficacy of Paxlovid for the claimed indication.

2.4.2 Safety Results

Safety data for Studies 1005 and 1002 was pooled as both studies represented a 5-day treatment regimen in patients with COVID-19. The proportion of participants with all-causality TEAEs that started on or prior to the Day 34 visit was comparable between treatment groups. The proportion of participants with TEAEs ≥ Grade 3 was lower in the Paxlovid group compared with the placebo group. Common TEAEs included dysgeusia (5.6%), diarrhea (3.3%) and vomiting(1.3%).

The overall incidence of participants with all-causality treatment-emergent SAEs that started on or prior to the Day 34 visit was lower in the Paxlovid group (1.6%) compared with the placebo group (5.0%). All of the 16 deaths occurred in the placebo group.

No new significant safety information was identified from post-marketing data in adults and pediatrics.

2.5 Bridging Study Evaluation

Following nirmatrelvir/ritonavir 250/100 mg BID for 10 days (PART-2 of Study C4671001), geometric mean dose normalized AUC_{tau} and C_{max} of nirmatrelvir at steady state was approximately 30% and 21%-26% lower in Japanese participants compared to those observed in non-Japanese participants across all days. Drug accumulation on Day 10 based on AUC_{tau} and C_{max} ratios was similar between the Japanese and non-Japanese participants. Slightly lower systemic exposures in Japanese subjects than those in Western subjects was not considered clinically meaningful. In a population PK analysis that included Japanese subjects from this study and from Phase 2/3 studies, race did not affect the PK of nirmatrelvir.

In the East Asian subpopulation of Study C4671005, 116 subjects were screened for entry into the study in sites from Japan, South Korea, Thailand, and Malaysia, of whom 112 were randomized and 109 were treated. In the East Asian subpopulation, treatment with Paxlovid reduced the proportion of subjects with COVID-19-related hospitalization or death from any cause through Day 28. Treatment with nirmatrelvir/ritonavir was demonstrated to be safe and well tolerated, and no distinct safety signals were seen between the overall population and East Asian subpopulation.

Further bridging study was waived.

2.6 Conclusion

This multidisciplinary review recommends approval for Paxlovid 150 mg/100 mg Film-coated Tablets (nirmatrelvir / ritonavir) for the treatment of adults and pediatric patients (12 years of age and older) with mild-to-moderate coronavirus disease 2019 (COVID-19) and

who are at high risk for progression to severe COVID-19.

3. Post-Marketing Requirements

NA