swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Paxlovid

International non-proprietary name:	nirmatrelvir, ritonavir
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	150 mg nirmatrelvir, 100 mg ritonavir
Route(s) of administration:	oral
Marketing authorisation holder:	Pfizer AG
Marketing authorisation no.:	68793
Decision and decision date:	extension of therapeutic indication approved on 27 March 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus Disease 2019
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Standard error
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Paxlovid is indicated for the treatment of Coronavirus Disease 2019 (COVID-19) in paediatric patients 6 years of age and older weighing at least 20 kg who do not require oxygen therapy or hospitalisation due to COVID-19, and who are at increased risk for progressing to severe COVID-19 (see "Clinical efficacy").
Paxlovid is not intended as a replacement for vaccination against COVID-19.
Paxlovid should be used in accordance with official recommendations and in consideration of local epidemiological data about circulating SARS-CoV-2 variants.

2.2.2 Approved indication

Paxlovid is indicated for the treatment of Coronavirus Disease 2019 (COVID-19) in paediatric patients 6 years of age and older weighing at least 20 kg who do not require oxygen therapy or hospitalisation due to COVID-19, and who are at increased risk for progressing to severe COVID-19 (see "Clinical efficacy").
Paxlovid is not intended as a replacement for vaccination against COVID-19.
Paxlovid should be used in accordance with official recommendations and in consideration of local epidemiological data about circulating SARS-CoV-2 variants.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose for paediatric patients ≥6 years of age weighing ≥40 kg is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days.
The recommended dose for paediatric patients ≥6 years of age weighing ≥20 to <40 kg is 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	3 March 2025
Formal objection	24 March 2025
Response to formal objection	28 March 2025
Formal control completed	2 April 2025
List of Questions (LoQ)	29 July 2025
Response to LoQ	26 September 2025
Preliminary decision	25 November 2025
Response to preliminary decision	6 February 2026
Final decision	27 March 2026
Decision	approval

3 Medical context

COVID-19 is a pandemic disease that started in Wuhan, China, in December 2019. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

COVID-19 clinical spectrum ranges from asymptomatic infection to severe disease. The majority of patients will present non-severe (flu-like syndrome) or mild symptoms (mild pneumonia). However, a subset of patients will present severe (important lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan dysfunction) that might ultimately lead to death. In particular, patients with risk factors (e.g. obesity, old age, chronic lung, kidney or heart disease, active cancer or immunosuppression, diabetes) are at elevated risk of severe course and death.

Severe SARS-CoV-2 infections are much less frequent in adolescents and small children than in adults. However, older children and adolescents can harbour comorbidities associated with worse outcomes. There is currently no approved outpatient oral treatment for the paediatric population in Switzerland.

4 Nonclinical aspects

4.1 Nonclinical conclusions

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to method of administration. The dosage for the paediatric population is the same or lower, depending on the patient's weight.

Based on the ERA, the indication extension will not be associated with a significant risk for the environment.

From the nonclinical point of view, there are no objections to approval of the proposed indication extension.

5 Clinical aspects

5.1 Clinical pharmacology

In paediatric patients aged ≥ 6 years, nirmatrelvir exposures at the proposed body-weight band-based dose (bodyweight ≥40 kg and ≥20 to <40 kg) were higher than the reference adult exposure. More than 90% of participants achieved a minimum observed concentration greater than the 90% effective concentration, regardless of bodyweight, age or dose. The ritonavir concentration in paediatric patients administered 100 mg ritonavir was generally in the same range as in adults.

5.2 Efficacy

The efficacy of nirmatrelvir/ritonavir in paediatric patients ≥6 years of age and weighing more than 20 kg who are at risk of progression to severe disease is supported by efficacy outcomes from studies in adults based on matching exposures in adults and children.

The applicant provided an interim clinical study report (CSR) from the open-label, single-arm study C4671026. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and efficacy of nirmatrelvir/ritonavir for the treatment of nonhospitalised, symptomatic paediatric participants with COVID-19 who were at risk of progression to severe disease.

This study is enrolling approximately 160 paediatric participants into 5 cohorts in a tiered scheme based on age and/or weight. In the interim CSR, results from 61 participants in Cohort 1 [≥6 to <18 years of age weighing ≥40 kg, stratified in 1a (≥12 to <18 years of age weighing ≥40 kg) and 1b (≥6 to <12 years of age weighing ≥40 kg)] and 14 participants in Cohort 2 (≥6 to <18 years of age weighing ≥20 to <40 kg) are presented. Approximately, half of the participants (54.5%) were not vaccinated. The vast majority of participants (80.5%) had 1 risk factor for progression to COVID-19 severe disease. The most frequently reported conditions in either cohort present at the start of the study were obesity (37 [49.3%] participants overall) and chronic respiratory disease (30 [40.0%] participants overall). Overall, median duration of symptoms before study inclusion was 1 day (range 0-4).

Clinical efficacy in study C4671026 was assessed as secondary and exploratory efficacy endpoints. It must be noted that this was an open-label study without a placebo arm and that the SARS-CoV-2 circulating variant during the study was Omicron. Clinical outcomes showed no COVID-19 hospitalisations or all-cause death through Day 28 in any participant. Median times to alleviation and resolution ranged from 5.0 to 10.0 days across cohorts and dose subgroups. No participants reported a severe sign or symptom after Day 14. Comparisons with the adult results are difficult to draw because of the differences in the collection of COVID-19 signs and symptoms. Virological outcomes showed reductions of SARS-CoV-2 viral load (adjusted mean (standard error (SE)) from baseline through Day 5 that that ranged from -3.395 (0.449) log10 copies/mL in Cohort 2 to -4.763 (0.567) log10 copies/mL in Cohort 1a 150 mg. The available kinetics data indicate that the reduction in SARS-CoV-2 viral load in the paediatric population is at least similar to that in the adult population. Two (2.7%) participants met the definition of SARS-CoV-2 viral RNA rebound at Day 10 or Day 14. The viral RNA rebound was associated with new or worsening COVID-19 signs/symptoms for 1 participant. Clinical virology data submitted does not indicate that nirmatrelvir/ritonavir treatment is associated with emergence of resistance in the paediatric population.

5.3 Safety

No new or unexpected safety issues arose in the paediatric population studied in comparison to what is known in the adult population. Most adverse events were mild or moderate and not related to the treatment. The safety analysis set consisted in 75 participants, 61 in Cohort 1 and 14 in Cohort 2. The most frequently reported TEAEs were diarrhoea and headache in 3 (4.0%) participants each and

vomiting, dizziness, cough in 2 (2.7%) participants each. One participant in Cohort 2 discontinued study intervention due to a nonserious AE of viral infection.

No treatment-related SAEs were reported during the study. However, the sample size of the study was small, so no definite conclusion on safety aspects can be made. No potential Hy's Law cases were identified but one incidence of Temple's Corollary was identified in Cohort 2, probably linked to the underlying COVID-19 disease.

Paxlovid tolerability was acceptable as exemplified by the fact that nearly all participants completed the 5-day course of treatment and no participant discontinued the study intervention due to treatment-related AEs.

5.4 Final clinical benefit risk assessment

The study did not include a control arm and there was a limited number of participants. Therefore, no firm conclusion on the clinical efficacy and safety of nirmatrelvir/ritonavir treatment can be drawn from these data, which are essentially supportive.

Extrapolation of efficacy from outcomes in adult studies was accepted for some other COVID-19 products on the basis of similarity of disease and similar exposure. Children generally exhibit milder disease than adults and severe clinical course is less frequent in the paediatric population, therefore the medical need in the paediatric population applied for is expected to be low. However, in a selected at-risk paediatric population the availability of an outpatient oral treatment patients fulfils an unmet need.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Paxlovid was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

This product information will be updated on a regular basis as further data and safety reports become available.

Paxlovid®

Composition

Active substances

Nirmatrelvirum (corresponds to the substance with the chemical name: (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); ritonavirum.

Excipients

Nirmatrelvir

Lactose monohydrate (185 mg), microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate, hypromellose, titanium dioxide, macrogol 400, iron oxide red.

Total sodium content per film-coated tablet: 0.99 mg.

Ritonavir

Copovidone, sorbitan laurate, colloidal silicon dioxide anhydrous, calcium hydrogen phosphate, sodium stearyl fumarate, hypromellose, titanium dioxide, macrogol 400, hydroxypropyl cellulose, talc, macrogol 3350, polysorbate 80.

Total sodium content per film-coated tablet: 0.39 mg.

Pharmaceutical form and active substance quantity per unit

Nirmatrelvir

Film-coated tablet.

1 nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir.

Pink, oval tablet, with a dimension of approximately 17.6 mm in length and 8.6 mm in width, debossed with «PFE» on one and «3CL» on the other side.

Ritonavir

Film-coated tablet.

1 ritonavir film-coated tablet contains 100 mg of ritonavir.

White to off white, capsule-shaped tablets, with a dimension of approximately 17.1 mm in length and 9.1 mm in width, debossed with «H» on one and «R9» on other side.

Indications/Uses

Paxlovid is indicated for the treatment of Coronavirus Disease 2019 (COVID-19) in adult and paediatric patients 6 years of age and older weighing at least 20 kg who do not require oxygen therapy or hospitalisation due to COVID-19, and who are at increased risk for progressing to severe COVID-19 (see «Clinical efficacy»).

Paxlovid is not intended as a replacement for vaccination against COVID-19.

Paxlovid should be used in accordance with official recommendations and in consideration of local epidemiological data about circulating SARS-CoV-2 variants.

Dosage/Administration

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets.

The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose.

Usual dosage

Adult patients

The recommended dose in adults is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours (in the morning and at bedtime) for 5 days.

Paediatric patients 6 years of age and older weighing at least 20 kg

The recommended dose in paediatric patients 6 years of age and older weighing at least 20 kg is shown below in Table 1.

Table 1: Recommended dose for paediatric patients 6 years of age and older weighing at least 20 kg

Patient Population	*Recommended Dose*
Paediatric patients ≥6 years of age weighing ≥40 kg	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days
Paediatric patients ≥6 years of age weighing ≥20 to <40 kg	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days

Special attention for paediatric patients 6 years of age and older weighing at least 20 kg to less than 40 kg

The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose for adult and paediatric patients 6 years of age and older weighing at least 40 kg.

Therefore, the caregiver of paediatric patients 6 years of age and older weighing at least 20 kg to less than 40 kg and the paediatric patient itself should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.

Paxlovid should be administered as soon as possible after a positive viral test for SARS-CoV-2 even if baseline COVID-19 symptoms are mild (see «Properties/Effects»). A test using the nucleic acid amplification technique (NAAT) is preferred for confirmation of COVID-19. At the discretion of the treating physician completion of the full 5-day treatment course is recommended even if the patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with Paxlovid.

Missed doses

If the patient misses a dose of Paxlovid within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Special dosage instructions

Patients with hepatic disorders

No dosage adjustment of Paxlovid is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Paxlovid should not be used in patients with severe (Child-Pugh Class C) hepatic impairment (see «Warnings and precautions» and «Pharmacokinetics»).

Patients with renal disorders

No dose adjustment is needed in patients with mild renal impairment [estimated glomerular filtration rate (eGFR) ≥60-<90 ml/min].

Although the safety and pharmacokinetics of Paxlovid have not been studied in paediatric patients with renal impairment, dose reduction in paediatric patients 6 years of age and older weighing at least 40 kg with renal impairment should parallel that recommended for adults with the same degree of renal impairment (see «Pharmacokinetics»).

In patients with moderate renal impairment (eGFR ≥30-<60 ml/min) or with severe renal impairment (eGFR <30 ml/min) including those requiring haemodialysis, the dosage of Paxlovid should be reduced as shown in Table 2. Paxlovid should be administered at approximately the same time each day for 5 days. On days patients with severe renal impairment undergo hemodialysis, the Paxlovid dose should be administered after haemodialysis (see «Pharmacokinetics»).

Table 2: Recommended dose and regimen for patients with moderate and severe renal impairment

Renal function	*Days of treatment with Paxlovid*	*Dose and dose frequency*[a]
Moderate renal impairment (eGFR ≥30 to <60 ml/min)	Days 1-5	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) **every 12 hours for 5 days**
Severe renal impairment (eGFR <30 ml/min) including those requiring haemodialysis[b]	Day 1	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) **once on day 1**
	Days 2-5	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) **once daily on days 2 to 5**

Abbreviation: eGFR = estimated glomerular filtration rate.
[a] Paxlovid should be administered at approximately the same time each day for 5 days.
[b] On days of haemodialysis, the Paxlovid dose should be administered after haemodialysis.

Special attention for patients with moderate renal impairment

The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose for adult and paediatric patients 6 years of age and older weighing at least 40 kg.

Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.

Special attention for patients with severe renal impairment

The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose.

Therefore, patients with severe renal impairment should be alerted on the fact that two tablets of nirmatrelvir with one tablet of ritonavir should be taken once on day 1 followed by one tablet of nirmatrelvir with one tablet of ritonavir once daily on days 2 to 5.

Dose in paediatric patients with renal impairment weighing less than 40 kg has not been determined.

Paediatric population

Paediatric dosing in patients 6 years of age and older weighing at least 20 kg is based on the safety, pharmacokinetic (PK), efficacy, and tolerability results from a paediatric study (see «Pharmacodynamics» and «Pharmacokinetics»).

The safety and efficacy of Paxlovid in paediatric patients below 6 years of age or paediatric patients 6 years of age and older weighing less than 20 kg have not been established.

Patients with other underlying disorders

Concomitant therapy with ritonavir- or cobicistat-containing regimen

No dose adjustment of Paxlovid is needed.

Patients receiving ritonavir- or cobicistat-containing therapy (e.g. for HIV treatment) should continue their treatment as indicated.

Mode of administration

For oral use.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir will result in plasma levels of this active substance that will be insufficient to achieve the desired therapeutic effect.

Paxlovid can be taken with or without food (see «Pharmacokinetics»). The tablets should be swallowed whole and not chewed, broken, or crushed, as no data is currently available.

Contraindications

Medicinal products that are highly dependent on CYP3A for clearance, and for which elevated concentrations are associated with serious and/or life-threatening reactions.

- α_1-Adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, encainide*, flecainide, propafenone*, quinidine*
- Anticoagulants: dabigatran
- Anti-gout: colchicine
- Antihistamines: astemizole*, terfenadine*
- Antipsychotics/neuroleptics: lurasidone, pimozide*, quetiapine
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine*, ergonovine*, ergotamine*, methylergonovine
- GI motility agents: cisapride*
- Immunosuppressants: voclosporin
- Lipid-modifying agents:
    - HMG Co-A reductase inhibitors: lovastatin*, simvastatin
    - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide*
- Migraine medications: eletriptan, ubrogepant*
- Mineralocorticoid receptor antagonists: finerenone
- Non-opioid analgesic (selective blocker of $Na_v1.8$ sodium channels): suzetrigine*
- Opioid antagonists: naloxegol
- PDE5 inhibitor: avanafil, sildenafil, tadalafil, vardenafil
- Sedative/hypnotics: clorazepate, diazepam, estazolam*, flurazepam, triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin*
- Vasopressin receptor antagonists: tolvaptan

* not approved in Switzerland

Medicinal products that are potent CYP3A inducers where significantly reduced nirmatrelvir/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and

possible resistance. Paxlovid cannot be started immediately after discontinuation of any of the following medicinal products due to the delayed offset of the recently discontinued CYP3A inducer (see «Interactions»).
A multi-disciplinary approach (e.g., involving physicians and specialists in clinical pharmacology) should be considered to determine the adequate timing for Paxlovid initiation taking into account the delayed offset of the recently discontinued CYP3A inducer and the need to initiate Paxlovid within 5 days of symptom onset.

- Anticancer drugs: neratinib, venetoclax, apalutamide, enzalutamide
- Antibiotics: fusidic acid, rifampicin, rifapentine*
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin, primidone
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John’s wort (*Hypericum perforatum*)

* not approved in Switzerland

Medicinal products listed above and in «Interactions» are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated with Paxlovid.

Hypersensitivity to the active substances or to any of the excipients listed in «Composition».

Warnings and precautions

Risk of serious adverse reactions due to interactions with other medicinal products

Initiation of Paxlovid, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid, may increase plasma concentrations of medicinal products metabolised by CYP3A.

Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of Paxlovid.
- Loss of therapeutic effect of Paxlovid and possible development of viral resistance.

Severe, life-threatening, and fatal adverse reactions due to drug interactions have been reported in patients treated with Paxlovid.

Table 3 lists drugs that are contraindicated or lead to significant interactions when used concomitantly with nirmatrelvir/ritonavir (see «Interactions»). The duration of the period of risk of interaction is not exactly known. Potential for interactions should be considered with other medicinal products prior to, during and after Paxlovid therapy; concomitant medicinal products should be reviewed during Paxlovid therapy, and the patient should be monitored for the adverse reactions associated with the concomitant medicinal products.

Co-administration of Paxlovid with calcineurin inhibitors and mTOR inhibitors
Consultation of a multidisciplinary group (e.g., involving physicians, specialists in immunosuppressive therapy, and/or specialists in clinical pharmacology) is required to handle the complexity of this co-administration by closely and regularly monitoring immunosuppressant blood concentrations and adjusting the dose of the immunosuppressant in accordance with the latest guidelines (see «Interactions»).

Hypersensitivity reactions

Anaphylaxis, hypersensitivity reactions, and serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported with Paxlovid (see «Undesirable effects»). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care.

Severe renal impairment

There are limited clinical safety data in patients with severe renal impairment (including patients with ESRD).

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, Paxlovid should not be used in patients with severe hepatic impairment.

Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Risk of HIV-1 resistance development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Excipients of particular interest

Nirmatrelvir film-coated tablets contain the excipient lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Nirmatrelvir and ritonavir film-coated tablets each contain less than 1 mmol sodium (23 mg) per dose, i.e., they are almost «sodium-free».

Interactions

Paxlovid (nirmatrelvir/ritonavir) is a strong CYP3A inhibitor and an inhibitor of CYP2D6, p-glycoprotein (P-gp) and OATP1B1. Co-administration of Paxlovid with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse reactions.

Paxlovid (nirmatrelvir/ritonavir) also exhibits strong affinity for CYP2C9.

Because of these properties, the drug has significant interaction potential and it is not possible to list all potential interaction partners by name here. In case of concomitant use of other medicinal products, therefore, it is always advisable to refer to their professional information in order to obtain information on their metabolization pathways and potential interactions as well as on the resulting possible risks and any dose adjustments (or other measures) that may be required.

Effects of Paxlovid on the pharmacokinetics of other medicinal products

Paxlovid (nirmatrelvir/ritonavir) is a strong inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first-pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with nirmatrelvir/ritonavir. Thus, coadministration of Paxlovid with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see Table 3).

Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 *in vitro* at clinically relevant concentrations. *In vitro* study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. The clinical relevance is unknown. Based on *in-vitro* data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 >CYP2D6. Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction (see Table 3) should be considered only if the benefits outweigh the risks.

As a conservative measure, the drug-drug interactions pertaining to ritonavir used in chronic HIV infection (600 mg BID when originally used as an antiretroviral agent and 100 mg BID as currently used as a pharmacokinetic enhancer with antiretroviral agents), should apply for Paxlovid. Future investigations may enable to adjust the recommendations related to drug-drug interactions to the 5 days treatment duration of Paxlovid.

Medicinal products listed in Table 3 are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated or may interact with nirmatrelvir/ritonavir and should be used with caution.

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
α1-adrenoreceptor antagonist	↑Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see «Contraindications»).
	↑Tamsulosin	Avoid concomitant use.
Amphetamine derivatives	↑Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are co-administered with Paxlovid.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
Analgesics	↑Buprenorphine (57%, 77%), ↑Norbuprenorphine (33%, 108%)	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when the two are dosed together.
	↓Pethidine (62%, 59%), ↑Norpethidine metabolite (47%, 87%)	The use of pethidine and ritonavir is contraindicated due to the increased concentrations of the metabolite norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects, e.g., seizures (see «Contraindications»).
	↓Piroxicam	Decreased piroxicam exposure due to CYP2C9 induction by Paxlovid.
	↑Fentanyl ↑Hydrocodone* ↑Oxycodone ↑Meperidine*	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with ritonavir. If concomitant use is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	↓Methadone (36%, 38%)	Monitor methadone-maintained patients closely for evidence of withdrawal effects. Increased methadone dose may be necessary when co-administered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓Morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as a pharmacokinetic enhancer.
Antianginal	↑Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see «Contraindications»).

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
Antiarrhythmics	↑Amiodarone, ↑Dronedarone, ↑Encainide*, ↑Flecainide, ↑Propafenone*, ↑Quinidine*	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, encainide, flecainide, propafenone and quinidine and is therefore contraindicated (see «Contraindications»).
	↑Disopyramide* ↑Lidocaine (systemic)	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
	↑Digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer. Caution should be exercised when co-administering Paxlovid with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Antiasthmatic	↓Theophylline (43%, 32%)	An increased dose of theophylline may be required when co-administered with ritonavir, due to induction of CYP1A2.
Anticancer agents	↑Afatinib	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) inhibition and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with Paxlovid (refer to the afatinib comprehensive information for professionals). Monitor for ADRs related to afatinib.
	↑Abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Coadministration of abemaciclib and Paxlovid should be avoided. If this coadministration is judged unavoidable, refer to the abemaciclib comprehensive information for professionals for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
	↑Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when co-administered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of Paxlovid with apalutamide is therefore contraindicated (see «Contraindications»).

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
	↑Ceritinib	Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with Paxlovid. Refer to the ceritinib comprehensive information for professionals for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑Dasatinib, ↑Nilotinib, ↑Vincristine, ↑Vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑Encorafenib ↑Ivosidenib*	Serum concentrations of encorafenib or ivosidenib may be increased when co-administered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Coadministration of encorafenib or ivosidenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	Enzalutamide	Enzalutamide is a strong CYP3A4 inducer, and this may lead to decreased exposure of Paxlovid, potential loss of virologic response, and possible resistance. Concomitant use of enzalutamide with Paxlovid is contraindicated (see «Contraindications»).
	↑Fostamatinib*	Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension, or diarrhoea. Refer to the fostamatinib product information for dose reduction recommendations if such events occur.
	↑Ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumor lysis syndrome. Coadministration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
	↑Neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with Paxlovid is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see «Contraindications»).
	↑Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase and is therefore contraindicated (see «Contraindications» and refer to the comprehensive information for professionals). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax comprehensive information for professionals for dosing instructions).
Anticoagulants	↑Rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.
	↑Dabigatran[b] (94%, 133%)	The concomitant use of Paxlovid and dabigatran is contraindicated.
	↑Apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with P-gp and strong CYP3A4 inhibitors depend on the apixaban dose. Refer to the apixaban product label for more information.
	↑Vorapaxar*	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The coadministration of vorapaxar with Paxlovid should be avoided.
	Warfarin*, ↑↓S-Warfarin (9%, 9%), ↓↔R-Warfarin (33%)	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation; therefore, it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ritonavir.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
Anticonvulsants	Carbamazepine[a], Phenobarbital, Phenytoin Primidone	Carbamazepine, phenobarbital, phenytoin and primidone are strong CYP3A4 inducers, and this may lead to a decreased exposure of nirmatrelvir and ritonavir and potential loss of virologic response. Concomitant use with Paxlovid is contraindicated (see «Contraindications»).
	↓Divalproex*, ↓Lamotrigine, ↓Phenytoin	Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are co-administered with ritonavir. Phenytoin may decrease serum levels of ritonavir. The concomitant use of Paxlovid and phenytoin is contraindicated (see «Contraindications»).
	Clonazepam	A dose decrease may be needed for clonazepam when co-administered, and clinical monitoring is recommended.
Antidepressants	↑Amitriptyline, ↑Fluoxetine, ↑Imipramine, ↑Nortriptyline*, ↑Paroxetine, ↑Sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see «Interactions»).
	↑Desipramine* (145%, 22%)	The AUC and C_{max} of the 2-hydroxy metabolite were decreased 15% and 67%, respectively. Dosage reduction of desipramine is recommended when co-administered with ritonavir.
Anti-gout	↑Colchicine	Concentrations of colchicine are expected to increase when co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with Paxlovid is contraindicated (see «Contraindications»).
Antihistamines	↑Astemizole* ↑Terfenadine*	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents and therefore,

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
		concomitant use with Paxlovid is contraindicated (see «Contraindications»).
	↑Fexofenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.
	↑Loratadine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is co-administered with ritonavir.
Anti-infectives	↑Rifabutin (4-fold, 2.5-fold) ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when co-administered with ritonavir as a pharmacokinetic enhancer.
	↓Voriconazole (39%, 24%)	Coadministration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
	↑Ketoconazole (oral) (3.4-fold, 55%)	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when co-administered with ritonavir.
	↑Itraconazole[a], ↑Erythromycin	Itraconazole increases the AUC and C_{max} of nirmatrelvir by 39% and 19%, respectively. Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is co-administered with ritonavir.
	↓Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is co-administered with ritonavir.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
	↑Bedaquiline*	No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, coadministration should be avoided. If the benefit outweighs the risk, coadministration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline Summary of Product Characteristics)
	Delamanid*	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see «Warnings and precautions» and refer to the delamanid product information).
	↑Clarithromycin (77%, 31%), ↓14-OH clarithromycin metabolite (100%, 99%)	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.
	Sulfamethoxazole/Trimetho-prim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
	↑Fusidic acid	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see «Contraindications»).
	Rifampicin/Rifapentin*	Rifampicin and rifapentine are strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
		virologic response. Concomitant use of rifampicin or rifapentine with Paxlovid is contraindicated (see «Contraindications»).
Antiparasitic agent	↓Albendazole	Significant decreases in plasma concentrations of albendazole and its active metabolite may occur due to induction by ritonavir, with a risk of decreased albendazole efficacy. Clinical monitoring of therapeutic response and possible adjustment of albendazole dosage during treatment with Paxlovid and following discontinuation is recommended.
Anti-HIV	↑Efavirenz (21%)	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir.
	↑Maraviroc (161%, 28%)	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Comprehensive information for professionals for maraviroc.
	↓Raltegravir (16%, 1%)	Coadministration of ritonavir and raltegravir results in a minor reduction in raltegravir levels.
	↓Zidovudine (25%, ND)	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.
	↑Atazanavir ↑Darunavir ↑Nevirapine ↑Tipranavir*	For further information, refer to the respective anti-HIV drug Comprehensive information for professionals.
	↑Bictegravir/ ↔Emtricitabine/ ↑Tenofovir	Ritonavir may significantly increase the plasma concentrations of bictegravir through CYP3A inhibition. Ritonavir is expected to increase the absorption of tenofovir alafenamide by inhibition of P-gp, thereby increasing the systemic concentration of tenofovir.
Anti-HCV	↑Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Avoid concomitant use of glecaprevir/pibrentasvir with Paxlovid. due to an increased risk of ALT elevations associated with increased glecaprevir exposure.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
	↑Sofosbuvir/velpatasvir/voxilaprevir	Serum concentrations may be increased due to OATP1B inhibition by ritonavir. Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and Paxlovid is not recommended. Refer to the sofosbuvir/velpatasvir/voxilaprevir Information for Professionals for further information.
Antipsychotics	↑Haloperidol, ↑Risperidone, ↑Thioridazine*	Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
	↑Lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see «Contraindications»).
	↑Pimozide*	Ritonavir coadministration is likely to result in increased plasma concentrations of pimozide and is therefore contraindicated (see «Contraindications»).
	↑Clozapine	Given the risk of substantial increase in clozapine exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
	↑Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of Paxlovid and quetiapine is contraindicated as it may increase quetiapine-related toxicity (see «Contraindications»).
β2-Agonists (long acting)	↑Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected. Avoid concomitant use with Paxlovid.
Benign prostatic hyperplasia agents	↑Silodosin	Coadministration contraindicated due to potential for postural hypotension (see «Contraindications»).

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
Calcium channel antagonist	↑Amlodipine, ↑Diltiazem, ↑Felodipine, ↑Nicardipine, ↑Nifedipine, ↑Verapamil	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.
	Lercandipine	Avoid concomitant administration of Paxlovid and lercandipine.
Cardiovascular agents	↑Aliskiren	Avoid concomitant use with Paxlovid.
	↑Eplerenone	Coadministration with eplerenone is contraindicated due to potential for hyperkalemia (see «Contraindications»).
	↑Ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see «Contraindications»).
	↑Ticagrelor ↑Vorapaxar* ↓Clopidogrel (Clopidogrel active metabolite)	Avoid concomitant use with Paxlovid.
	↑Cilostazol*	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	↑Betamethasone, ↑Budesonide, ↑Ciclesonide, ↑Dexamethasone, ↑Fluticasone, ↑Methylprednisolone, ↑Mometasone, ↑Triamcinolone	Coadministration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	Lumacaftor/ivacaftor	Coadministration contraindicated due to potential loss of virologic response and possible resistance (see «Contraindications»).
	↑Ivacaftor ↑Elexacaftor/tezacaftor/ivacaftor ↑Tezacaftor/ivacaftor	Reduce dosage when co-administered with Paxlovid. Refer to individual product labels for more information.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
Dipeptidyl peptidase 4 (DPP4) inhibitors	↑Saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.
Endothelin antagonists	↑Bosentan	Coadministration of bosentan and ritonavir may increase steady state bosentan maximum concentrations (C_{max}) and AUC. Discontinue use of bosentan at least 36 h prior to initiation of Paxlovid. Refer to the bosentan product label for further information.
Ergot derivatives	↑Dihydroergotamine*, ↑Ergonovine*, ↑Ergotamine*, ↑Methylergonovine	Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see «Contraindications»).
GI motility agent	↑Cisapride*	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent and therefore concomitant use with Paxlovid is contraindicated (see «Contraindications»).
Herbal products	St. John's Wort	Herbal preparations containing St John's wort (*Hypericum perforatum*): due to the risk of decreased plasma concentrations and reduced clinical effects of nirmatrelvir and ritonavir concomitant use with Paxlovid is contraindicated (see «Contraindications»).
HMG Co-A reductase inhibitors	↑Lovastatin*, ↑Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see «Contraindications»). Discontinue use of lovastatin and simvastatin at least 12 h prior to initiation of Paxlovid, during the 5 days of Paxlovid treatment and for 5 days after completing Paxlovid.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
	↑Atorvastatin, ↑Rosuvastatin	Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. Atorvastatin and rosuvastatin do not need to be halted prior to or after completing Paxlovid.
	↑Fluvastatin, ↑Pravastatin	The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.
Hormonal contraceptive	↓Ethinyl Estradiol (40%, 32%)	A barrier or other non-hormonal methods of contraception during the 5 days of Paxlovid treatment and until one menstrual cycle after stopping Paxlovid should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.
Immunosuppressants	Calcineurin inhibitors: ↑Cyclosporine ↑Tacrolimus	Avoid concomitant use of calcineurin inhibitors and mTOR inhibitors during treatment with Paxlovid.
	mTOR inhibitors: ↑Everolimus ↑Sirolimus	If this is not possible, dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions are recommended during and after treatment with Paxlovid. Refer to the individual immunosuppressant product label and latest guidelines for further information and obtain expert consultation of a multidisciplinary group (see «Warnings and precautions»).
	↑Voclosporine	Coadministration contraindicated due to potential for acute and/or chronic nephrotoxicity (see «Contraindications»).

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
Janus kinase (JAK) inhibitors	↑Tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
	↑Upadacitinib	Dosing recommendations for coadministration of upadacitinib with Paxlovid depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Lipid-modifying agents	↑Lomitapide*	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of Paxlovid with lomitapide is contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions (see «Contraindications»).
Migraine medications	↑Eletriptan	Coadministration of eletriptan within at least 72 h of Paxlovid is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events (see «Contraindications»).
	↑Rimegepant	Avoid concomitant use.
	↑Ubrogepant*	Coadministration of ubrogepant is contraindicated due to potential for serious adverse reactions (see «Contraindications»).
Mineralocorticoid receptor antagonists	↑Finerenone	Coadministration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia (see «Contraindications»).
Muscarinic receptor antagonists	↑Darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with Paxlovid. Refer to the darifenacin product label for more information.
	↑Solifenacin	The solifenacin daily dose should not exceed 5 mg when co-administered with Paxlovid. Refer to the solifenacin Information for Professionals for more information.
Neuropsychiatric agents	↑Suvorexant*	Avoid concomitant use of suvorexant.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
	↑Aripiprazole ↑Brexpiprazole ↑Cariprazine ↑Iloperidone* ↑Lumateperone* ↑Pimavanserin*	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.
Non-opioid analgesic (selective blocker of $Na_v1.8$ sodium channels)	↑Suzetrigine* and active metabolite M6-SUZ	Coadministration contraindicated due to potential for serious and/or life-threatening suzetrigine adverse reactions (see «Contraindications»).
Opioid antagonists	↑Naloxegol	Coadministration contraindicated due to the potential for opioid withdrawal symptoms (see «Contraindications»).
Phosphodiesterase (PDE5) inhibitors	↑Avanafil (13-fold, 2.4-fold)	As a safe and effective avanafil dosage regimen has not been established, concomitant use of avanafil with Paxlovid is contraindicated (see «Contraindications»).
	↑Sildenafil (11-fold, 4-fold)	Concomitant use of sildenafil with Paxlovid is contraindicated (see «Contraindications»).
	↑Tadalafil (124%, ↔)	Concomitant use of tadalafil with Paxlovid is contraindicated (see «Contraindications»).
	↑Vardenafil (49-fold, 13-fold)	Concomitant use of vardenafil with Paxlovid is contraindicated (see «Contraindications»).
Sedatives/hypnotics	↑Clorazepate, ↑Diazepam, ↑Estazolam*, ↑Flurazepam,	Ritonavir coadministration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore contraindicated (see «Contraindications»).
	↑Buspirone* ↑Zolpidem (28%, 22%)	A dose decrease and monitoring for adverse events may be needed for these drugs when co-administered with Paxlovid.
	↑Oral (1330%, 268%) and parenteral midazolam[b]	Midazolam is extensively metabolised by CYP3A4. Coadministration with Paxlovid may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, Paxlovid should not be co-administered with orally administered midazolam (see «Contraindications»), whereas caution should be used with coadministration of Paxlovid and parenteral midazolam. Data from concomitant use of parenteral

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
		midazolam with other protease inhibitors suggests a possible 3-4-fold increase in midazolam plasma levels. If Paxlovid is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
	↑Triazolam (> 20-fold, 87%)	Ritonavir coadministration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see «Contraindications»).
	↑Alprazolam (2.5-fold, ↔)	Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	↑Flibanserin*	Coadministration contraindicated due to potential for hypotension, syncope, and CNS depression (see «Contraindications»).
Smoke cessation	↓Bupropion (22%, 21%)	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir coadministration.
Soluble guanylate cyclase (sGC) stimulator	↑Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. Dosage adjustment is recommended for riociguat. Refer to the

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Comments*
		riociguat product label for more information.
Thyroid hormone replacement therapy	Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.
Vasopressin receptor antagonists	↑Tolvaptan	Coadministration contraindicated due to potential for dehydration, hypovolemia, and hyperkalaemia (see «Contraindications»).

Abbreviations: ALT = alanine aminotransferase
* not approved in Switzerland
[a] see «Interactions» Table 5
[b] see «Interactions» Table 4

The effects of co-administration of Paxlovid with midazolam (CYP3A4 substrate), dabigatran (P-gp substrate), or rosuvastatin (OATP1B1 substrate) on the midazolam, dabigatran, and rosuvastatin AUC_{inf} and C_{max}, respectively, are summarized in Table 4.

Table 4: Effect of nirmatrelvir/ritonavir on pharmacokinetics of co-administered drug

Co-administered drug	*Dose (schedule)*		*N*	*Percent ratio[a] of test/reference of geometric means (90% CI); no effect = 100*	
	Co-administered	*nirmatrelvir/ ritonavir*		*C_{max}*	*AUC_{inf}*
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (4 doses)	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)
Rosuvastatin[b]	10 mg (1 dose)	300 mg/100 mg twice daily (3 doses)	12	212.44 (174.31, 258.90)	131.18 (115.89, 148.48)

Abbreviations: AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma concentrations; CYP3A4 = cytochrome P450 3A4; OATP1B1 = organic anion transporting polypeptide 1B1; P-gp = P-glycoprotein.
[a] Percent ratio of test (i.e., midazolam, dabigatran, or rosuvastatin in combination with nirmatrelvir/ritonavir)/reference (i.e., midazolam, dabigatran, or rosuvastatin alone).
[b] For midazolam, Test = nirmatrelvir/ritonavir plus midazolam, Reference = midazolam. Midazolam is an index substrate for CYP3A4. For dabigatran, Test = nirmatrelvir/ritonavir plus dabigatran, Reference = dabigatran. Dabigatran is an index substrate for P-gp. For rosuvastatin, Test = nirmatrelvir/ritonavir plus rosuvastatin, Reference = rosuvastatin. Rosuvastatin is an index substrate for OATP1B1.

Effects of other medicinal products on pharmacokinetics of Paxlovid

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, medicinal products that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce Paxlovid therapeutic effect.

The effects of coadministration of Paxlovid with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarised in Table 5 (Effects of other drugs on nirmatrelvir).

Table 5: Interactions with other medicinal products: pharmacokinetic parameters for nirmatrelvir in the presence of the co-administered medicinal products

Co-administered medicinal product	*Dose (schedule)*		*N*	*Percent ratio of nirmatrelvir[a] pharmacokinetic parameters (90% CI); no effect = 100*	
	Co-administered medicinal product	*Nirmatrelvir/ ritonavir*		*C_{max}*	*AUC[b]*
Carbamazepine[c]	300 mg twice daily (16 doses)	300 mg/100 mg once daily (2 doses)	10	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC = area under the plasma concentration-time curve; CI = confidence interval; C_{max} = observed maximum plasma concentrations.
[a] Percent ratio of test (i.e., carbamazepine or itraconazole in combination with nirmatrelvir/ritonavir)/reference (i.e., nirmatrelvir/ritonavir alone).
[b] For carbamazepine, AUC = AUC_{inf}, for itraconazole, AUC = AUC_{tau}.
[c] Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

Pregnancy, lactation

Women of childbearing potential

There are limited data on the use of Paxlovid in pregnant women to inform the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid and for 7 days after completing Paxlovid.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with Paxlovid, and until one menstrual cycle after stopping Paxlovid (see «Interactions»).

Pregnancy

There are limited data from the use of Paxlovid in pregnant women.

There was no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability at any dose tested in rat or rabbit embryo-foetal developmental toxicity studies although lower foetal body weights were observed in rabbit. There were no nirmatrelvir-related adverse effects in a pre- and postnatal developmental study in rats (see «Preclinical data»).

A large number of women exposed to ritonavir during pregnancy indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems.

Animal data with ritonavir have shown reproductive toxicity (see «Preclinical data»).

Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception unless the clinical condition requires treatment with Paxlovid.

Lactation

In a clinical pharmacokinetics study, 8 healthy lactating women who were at least 12 weeks postpartum were administered 3 doses (steady-state dosing) of 300 mg/100 mg nirmatrelvir/ritonavir. Nirmatrelvir and ritonavir were excreted in breastmilk in small amounts, with a milk to plasma AUC ratio of 0.26 and 0.07, respectively. The estimated daily infant dose (assuming average milk consumption of 150 ml/kg/day), was 1.8% and 0.2% of the maternal dose.

There are no available data on the effects of nirmatrelvir or ritonavir on the breast-fed newborn/infant or on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Paxlovid and for 48 hours after completing Paxlovid treatment.

Fertility

There are no human data on the effect of Paxlovid (nirmatrelvir and ritonavir) or ritonavir alone on fertility.

Both nirmatrelvir and ritonavir, tested separately, produced no effects on fertility in rats (see «Preclinical data»).

Effects on ability to drive and use machines

Paxlovid is expected to have no influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

Adult population

The safety of Paxlovid was based on data from two Phase 2/3 randomized, placebo-controlled trials in adult participants 18 years of age and older (see «Pharmacodynamics»):

- Study C4671005 (EPIC-HR) and Study C4671002 (EPIC-SR) investigated Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) every 12 hours for 5 days in symptomatic participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Participants were to present with mild-to-moderate COVID-19 at baseline.

Across the two studies, 1'692 participants received a dose of Paxlovid, and 1'687 participants received a dose of placebo. The most common adverse reactions (≥1% incidence in the Paxlovid group) were dysgeusia (5.4% and 0.2%, respectively) and diarrhoea (3.4% and 2.1%, respectively).

The safety profile of Paxlovid in participants with severe renal impairment, including those requiring haemodialysis, was consistent with the safety profile observed in the placebo-controlled trials.

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows: «Very common» (≥1/10); «common» (≥1/100, <1/10); «uncommon» (≥1/1,000, <1/100); «rare» (≥1/10,000, <1/ 1,000); «very rare» (<1/10,000); «not known» (frequency cannot be estimated from the available data).

Table 6: Adverse drug reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Immune system disorders	Uncommon Not known	Hypersensitivity* Anaphylaxis*
Nervous system disorders	Common	Dysgeusia, headache
Vascular disorders	Uncommon	Hypertension
Gastrointestinal disorders	Common Uncommon	Diarrhoea, nausea*, vomiting Abdominal pain*
Skin and subcutaneous tissue disorders	Rare	Toxic epidermal necrolysis*, Stevens-Johnson syndrome*
General disorders and administration site conditions	Not known	Malaise*

* Adverse drug reaction (ADR) identified post-marketing

Description of specific adverse reactions and additional information

In study EPIC-HR, numerically higher myalgia and hypertension related adverse events were observed.

Paediatric population
The safety of Paxlovid in paediatric patients was evaluated in a Phase 2/3, open-label, single-arm study (see «Pharmacodynamics»).
In the study analysis, 75 participants 6 to less than 18 years of age weighing at least 20 kg were included in the assessment of safety. The adverse reaction profile observed in this study is similar to that in the adult population.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Treatment of overdose with Paxlovid should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Paxlovid.

Properties/Effects

ATC code

J05AE30

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of the SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.

Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

Antiviral activity

In-vitro antiviral activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection of differentiated normal human bronchial epithelial (dNHBE) cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7 (P252L+F294L), BF.7 (T243I), BQ.1.11, BQ.1, XBB.1.5, EG.5, and JN.1 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 88 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.8 relative to the USA-WA1/2020 isolate.
In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.

Antiviral resistance in cell culture and biochemical assays

SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 7 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 7: SARS-CoV-2 M^{pro} amino acid substitutions selected by nirmatrelvir in cell culture

Single substitution (EC_{50} value fold change)	T21I (1.1-4.8), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), und T304I (1.4-5.5).
≥2 substitutions (EC_{50} value fold change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1-8.9), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

Abbreviations: ND = no data (substitution emerged from nirmatrelvir resistance selection, but has not been tested for EC_{50} determination in an antiviral assay).

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced activity (fold-change based on Ki values) of nirmatrelvir: Y54A (25), F140A (21), F140L (7.6), F140S (230), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7700), P168del (9.3), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11000), T21I+A173V (15), L50F+E166V (4500), E55L+S144A (56), T135I+T304I (5.1), F140L+A173V (95), S144A+T304I (28), E166V+L232R (5700), P168del+A173V (170), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (180), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (1.5), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

Most single and some double M^{pro} amino acid substitutions identified which reduced the susceptibility of SARS-CoV-2 to nirmatrelvir resulted in an EC_{50} shift of <5-fold compared to wild type SARS-CoV-2 in an antiviral cell assay. Virus containing E166V shows the greatest reduction in susceptibility to nirmatrelvir and appears to have replication defect since it either could not be generated or had a very low virus titer. In general, triple and some double M^{pro} amino acid substitutions led to EC_{50} changes of >5-fold to that of wild type. The clinical significance needs to be further understood, particularly in the context of nirmatrelvir high clinical exposure (≥5× EC_{90}). Thus far, these substitutions have not been identified as treatment-emergent substitutions associated with hospitalization or death from the EPIC-HR or EPIC-SR studies.

Treatment-emergent substitutions were evaluated among participants in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n = 907 Paxlovid-treated participants, n = 946 placebo-treated participants). SARS-CoV-2 M^{pro} amino acid changes were

classified as Paxlovid treatment-emergent substitutions if they were absent at baseline, occurred at the same amino acid position in 3 or more Paxlovid-treated participants and were ≥2.5-fold more common in Paxlovid-treated participants than placebo-treated participants post-dose. The following Paxlovid treatment-emergent M^{pro} substitutions were observed: T98I/R/del (n = 4), E166V (n = 3), and W207L/R/del (n = 4). Within the M^{pro} cleavage sites, the following Paxlovid treatment-emergent substitutions were observed: A5328S/V (n = 7) and S6799A/P/Y (n = 4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in Paxlovid-treated participants who experienced hospitalization. Thus, the clinical significance of these substitutions is unknown.

Viral load rebound

Post-treatment increases in SARS-CoV-2 nasal RNA levels (i.e., viral RNA rebound) were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment nasal viral RNA rebound varied according to analysis parameters but was generally similar among Paxlovid and placebo recipients. A similar or smaller percentage of placebo recipients compared to Paxlovid recipients had nasal viral RNA results <lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of Paxlovid treatment. The clinical relevance of post-treatment increases in viral RNA following Paxlovid or placebo treatment is unknown.

EPIC-HR and EPIC-SR were not designed to evaluate symptomatic viral RNA rebound, and most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed). The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among Paxlovid and placebo recipients.

Cross-resistance

Cross-resistance between nirmatrelvir and other anti-SARS-CoV-2 agents that are not M^{pro} inhibitors is not expected.

Pharmacodynamics

Cardiac electrophysiology

At 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

Effects on viral RNA levels

Changes from baseline relative to placebo at Day 5 in viral RNA levels in nasopharyngeal samples are summarized by study in Table 8.

Table 8: Analysis of change from baseline to Day 5 in log_{10} (viral RNA levels, copies/ml); EPIC-HR and EPIC-SR (mITT1 analysis set)

	EPIC-HR (mITT1[a])		*EPIC-SR (mITT1[b])*	
	Paxlovid	*Placebo*	*Paxlovid*	*Placebo*
Primary VoC[c]	*Delta (99%)*		*Delta (79%) Omicron (19%)*	
Baseline	n = 764	n = 784	n = 542	n = 514
Median	6.075	5.990	6.615	6.430
Mean (SD)	5.780 (2.077)	5.617 (2.143)	6.214 (1.794)	6.045 (1.862)
Day 5	n = 676	n = 683	n = 498	n = 473
Median change from baseline	-2.990	-2.160	-3.680	-2.630
Median reduction relative to placebo	-0.830		-1.050	
Adjusted change from baseline, mean (95% CI)	-3.087 (-3.219, -2.955)	-2.310 (-2.439, -2.180)	-3.419 (-3.584, -3.253)	-2.551 (-2.723, -2.378)
Reduction relative to placebo, mean (95% CI)	-0.777 (-0.937, -0.617)		-0.868 (-1.073, -0.663)	
p-value	<0.0001		<0.0001	

Abbreviations: CI = confidence interval; COVID-19 = Coronavirus Disease 2019; mAb = monoclonal antibody; mITT = modified intent-to-treat; RT-PCR = reverse transcriptase–polymerase chain reaction; SD = standard deviation; VoC = variant of concern.

[a] All treated participants with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.

[b] All treated participants with at least 1 post-baseline visit through Day 28; 57% of these participants were vaccinated against COVID-19 at baseline.

[c] VoC lineage percentage relates to the entire study populations for EPIC-HR and EPIC-SR.

The degree of reduction in viral RNA levels relative to placebo following 5 days of Paxlovid treatment was similar across studies, including those enrolling unvaccinated participants (EPIC-HR) and those enrolling both unvaccinated and vaccinated participants (EPIC-SR).

Effect on lipids

The changes in lipids in nirmatrelvir/ritonavir treated group were not statistically different than placebo/ritonavir treated group in an exploratory analysis of lipids in multiple ascending dose cohorts

in which healthy participants were randomized to receive either escalating doses (75, 250 and 500 mg) of nirmatrelvir (n = 4 per cohort) or placebo (n = 2 per cohort), enhanced with ritonavir 100 mg, twice a day for 10 days.

In participants receiving placebo/ritonavir twice a day, a modest increase in cholesterol (≤27.2 mg/dl), LDL cholesterol (≤23.2 mg/dl), triglycerides (≤64.3 mg/dl) and decrease in HDL cholesterol (≤4 mg/dl) was observed. The clinical significance of such changes with short term treatment is unknown.

Clinical efficacy

Efficacy in adult participants at high risk of progressing to severe COVID-19 illness (EPIC-HR)

The efficacy of Paxlovid is based on the interim analysis and the supporting final analysis of EPIC-HR, a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection.

Eligible participants were 18 years of age and older with at least one of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities.

Participants with COVID-19 symptom onset of ≤5 days were included in the study. The study excluded individuals with a history of prior COVID-19 infection or vaccination.

Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir 300 mg/ritonavir 100 mg) or placebo orally every 12 hours for 5 days. The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2113 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 45 years with 12% of participants 65 years of age and older (3% were 75 years of age and older); 51% were male; 71% were White, 4% were Black or African American, and 15% were Asian; 41% were Hispanic or Latino; 67% of participants had onset of symptoms ≤3 days before initiation of

study treatment; 80% had a BMI ≥25 kg/m^2 (36% a BMI ≥30 kg/m^2); 11% had diabetes mellitus; less than 1% of the study population had immune deficiency, 49% of participants were serological negative at baseline and 49% were serological positive. The mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/ml (2.89); 27% of participants had a baseline viral load of >10^7 (copies/ml); 6% of participants either received or were expected to receive COVID-19 therapeutic mAb treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses. The primary SARS-CoV-2 variant across both treatment arms was Delta (99%), mostly clade 21J.

The baseline demographic and disease characteristics were balanced between the Paxlovid and placebo groups.

Table 9 provides results of the primary endpoint in the mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for Paxlovid compared to placebo was 86% (95% CI: 72%, 93%).

Table 9: Efficacy results in non-hospitalised adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 mAb treatment at baseline (mITT1 analysis set)

	Paxlovid (N = 977)	**Placebo (N = 989)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%) Reduction relative to placebo[a] [95% CI], %	9 (0.9%) -5.64 (-7.31, -3.97)	64 (6.5%)
p-value	<0.0001	
All-cause mortality through Week 24, %	0	15 (1.5%)

Abbreviations: CI = confidence interval, N = number of patients, mAb = monoclonal antibody.
[a] The estimated cumulative proportion of participants hospitalised or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalisation and death status through Day 28 were censored at the time of study discontinuation.

The estimated risk reduction was -6.1% with 95% CI of (-8.2%, -4.1%) in participants dosed within 3 days of symptom onset, and –4.6% with 95% CI of (-7.4%, -1.8%) in the mITT1 subset of participants dosed >3 days from symptom onset.

Consistent results were observed in the final mITT and mITT2 analysis populations. A total of 1’318 subjects were included in the mITT analysis population. The event rates were 5/671 (0.75%) in the Paxlovid group, and 44/647 (6.80%) in the placebo group.

Results from subgroup analyses were consistent with those in the overall population regardless of baseline serology status (Table 10).

Table 10: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set

	Paxlovid 300 mg/100 mg	**Placebo**
Number of patients	977	989
Serology Negative	n = 475	n = 497
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI], % p-value	8 (1.7%) 1.72 (0.86, 3.40) -9.79 (-12.86, -6.72) p<0.0001	56 (11.3%) 11.50 (8.97, 14.68)
Serology Positive	n = 490	n = 479
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI], % p-value	1 (0.2%) 0.20 (0.03, 1.44) -1.5 (-2.70, -0.25) p = 0.0180	8 (1.7%) 1.68 (0.84, 3.33)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat. All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤5 days after COVID-19 symptom onset.
Seropositivity was defined if results were positive in a serological immunoassay specific for host antibodies to either S or N viral proteins.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.
[a.] COVID-19 related hospitalisation or death from any cause.

Efficacy results for mITT1 were consistent across subgroups of participants including age (≥65 years) and BMI (BMI >25 and BMI >30) and diabetes.

Efficacy in paediatric participants with risk factors for progression to severe COVID-19 illness (EPIC-PEDS)

Paxlovid was evaluated in a Phase 2/3, open-label, single-arm study investigating the safety, pharmacokinetics, tolerability, and efficacy in non-hospitalised symptomatic paediatric participants with confirmed COVID-19 who are at risk of progression to severe disease. Efficacy in paediatric patients is primarily based on matching exposure to adult COVID-19 patients. The proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 is a supportive secondary endpoint. There have been no reports of COVID-19 related hospitalisation or death from any cause in this study.

Data are available from 75 participants 6 to less than 18 years of age weighing at least 20 kg who received Paxlovid (nirmatrelvir/ritonavir 150 mg/100 mg or 300 mg/100 mg) orally every 12 hours for 5 days. The most frequently reported risk factors at baseline for progression to severe disease were obesity (49%) and chronic lung disease (40%).

Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy participants and in participants with mild to moderate COVID-19.

Ritonavir is administered with nirmatrelvir as a PK enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir.

Upon repeat-dose of nirmatrelvir/ritonavir 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg administered twice daily, the increase in systemic exposure at steady-state is less than dose proportional. Multiple dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 were similar to Day 10 across all doses. Simulated repeat-dose exposures of nirmatrelvir/ritonavir 300 mg/100 mg administered twice daily in adult participants from EPIC-HR, suggested the mean AUC_{tau} was 28.3 µg*h/ml, mean C_{max} was 3.30 µg/ml, and mean C_{min} was 1.39 µg/ml.

Absorption

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean nirmatrelvir C_{max} and AUC_{inf} was 2.21 µg/ml and 23.01 µg*h/ml, respectively. The median time to C_{max} (T_{max}) was 3.00 h.

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir C_{max} and AUC_{inf} was 0.36 µg/ml and 3.60 µg*h/ml, respectively. The median time to C_{max} (T_{max}) was 3.98 h.

Effect of food on oral absorption

Dosing with a high fat meal increased the exposure of nirmatrelvir (approximately 61% increase in mean C_{max} and 20% increase in mean AUC_{last}) relative to fasting conditions following administration of 300 mg nirmatrelvir (2 × 150 mg) and 100 mg ritonavir tablets.

Distribution

The protein binding of nirmatrelvir in human plasma is approximately 69%.
The protein binding of ritonavir in human plasma is approximately 98-99%.

Metabolism

In vitro studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolised by CYP3A4. Administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, the only medicinal product-related entity observed following concomitant administration with ritonavir was unchanged nirmatrelvir.

In vitro studies utilising human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of oxidation metabolite M-2.

Elimination

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact medicinal product. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively. Nirmatrelvir was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta.

Following oral administration of a single dose of nirmatrelvir/ritonavir 300 mg/100 mg the arithmetic mean terminal elimination half-life of nirmatrelvir was 6.1 h.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir.

Following oral administration of a single dose of nirmatrelvir/ritonavir 300 mg/100 mg the arithmetic mean terminal elimination half-life of ritonavir was 6.1 h.

Kinetics in specific patient groups

Hepatic impairment

Compared to healthy controls with no hepatic impairment, the PK of nirmatrelvir in subjects with moderate hepatic impairment was not significantly different. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) was 98.78% (70.65%, 138.12%) and 101.96% (74.20%, 140.11%), respectively.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Renal impairment

Compared to healthy controls with no renal impairment, the pharmacokinetics of nirmatrelvir in adult participants with mild renal impairment were not significantly different. However, in the moderately and severely impaired adult participants the ratios of the adjusted geometric means (90% CI) for nirmatrelvir AUC_{inf} were 187.40% (148.52%, 236.46%) and 304.49% (237.6%, 390.21%), respectively compared to the healthy control group.

Patients with severe renal impairment including those requiring haemodialysis

The pharmacokinetics of nirmatrelvir in participants with mild-to-moderate COVID-19 and severe renal impairment (eGFR <30 ml/min) either requiring haemodialysis (n=12) or not requiring haemodialysis (n=2) were evaluated after administration of 300 mg/100 mg nirmatrelvir/ritonavir once on Day 1 followed by 150 mg/100 mg nirmatrelvir/ritonavir once daily on Days 2-5 for a total of 5 doses.

During a 4-hour haemodialysis session, approximately 6.9% of nirmatrelvir dose was cleared through dialysis. Haemodialysis clearance was 1.83 l/h.

Population pharmacokinetic model-based simulations showed that administration of 300 mg/100 mg nirmatrelvir/ritonavir once on Day 1 followed by 150 mg/100 mg nirmatrelvir/ritonavir once daily on Days 2-5 in participants with severe renal impairment resulted in comparable exposures on Day 1 and at steady-state (AUC_{0-24} and C_{max}) to those observed in participants with normal renal function receiving 300 mg/100 mg nirmatrelvir/ritonavir twice daily for 5 days.

Based on the results of population PK model-based simulation, dose reduction in paediatric patients 6 years of age and older weighing at least 40 kg with renal impairment should parallel that recommended for adults with the same degree of renal impairment.

Dose in paediatric patients with renal impairment weighing less than 40 kg has not been determined.

Age and gender

In a population PK analysis, age and gender did not affect the pharmacokinetics of nirmatrelvir.

Paediatric population

The pharmacokinetics of nirmatrelvir following nirmatrelvir/ritonavir 150 mg/100 mg or 300 mg/100 mg dosing twice daily have been evaluated in 68 paediatric participants 6 years of age and older weighing at least 20 kg (see «Pharmacodynamics»).

Population pharmacokinetic analyses and model-based simulation demonstrated that the C_{max}, AUC_{tau}, and C_{min} values of nirmatrelvir in paediatric participants 6 years of age and older (Table 11, dosing refer to table 11) were 1.3, 1.3, and 1.4-fold higher compared to adults. The recommended paediatric dosing regimens in participants 6 years of age and older weighing at least 20 kg result in no clinically relevant differences in systemic exposure to those in adults receiving nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days (see «Dosage/Administration»).

Table 11: Pharmacokinetic parameters of nirmatrelvir on Day 5 estimated using population PK modeling following administration of recommended paediatric nirmatrelvir/ritonavir dosing regimens[b]

Patient Population	*Paediatric Dose*	*C_{max} (µg/ml)[a]*	*AUC_{tau} (µg*h/ml)[a,c]*	*C_{min} (µg/ml)[a]*
Paediatric participants ≥6 years of age weighing ≥40 kg	300 mg nirmatrelvir/100 mg ritonavir twice daily for 5 days	4.10 (1.91, 8.86)	36.6 (13.3, 95.6)	1.91 (0.43, 6.93)
Paediatric participants ≥6 years of age weighing ≥20 to <40 kg	150 mg nirmatrelvir/100 mg ritonavir twice daily for 5 days	4.24 (2.00, 9.08)	37.3 (13.5, 98.1)	1.90 (0.40, 7.03)

Abbreviations: C_{max} = predicted maximal concentration; C_{min} = predicted minimal concentration (C_{trough}).
[a] Data presented as geometric mean (10^{th} and 90^{th} percentile).
[b] Data presented were generated using a population PK model simulation of 10'000 virtual subjects in each group.
[c] AUC_{tau} = predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice daily dosing.

There is insufficient information to assess the exposure of Paxlovid in paediatric patients weighing less than 20 kg.

In paediatric patients 6 years of age and older and weighing 20 kg, ritonavir concentrations after 100 mg ritonavir administration were mostly within the exposure measured in adults.

Ethnical origin

Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants. In a population PK analysis, race did not affect the pharmacokinetics of nirmatrelvir.

Preclinical data

No nonclinical safety studies have been conducted with nirmatrelvir in combination with ritonavir.

Repeated dose toxicity

Studies of repeated dose toxicity revealed no risk due to nirmatrelvir.

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland, and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation

of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinuria were noted in rats and are considered to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Genotoxicity

Studies of genotoxicity revealed no risk due to nirmatrelvir.

Genotoxicity studies revealed no risk due to ritonavir.

Carcinogenicity

No carcinogenicity studies have been conducted with nirmatrelvir.

Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumorigenic potential specific for these species but are regarded as of no relevance for humans.

Reproductive toxicity

Nirmatrelvir

No adverse effects were observed in fertility and embryo-foetal development studies in rats. A study in pregnant rabbits showed an adverse decrease in foetal body weight, in the absence of significant maternal toxicity. Systemic exposure (AUC_{24}) in rabbits at the maximum dose without adverse effect in foetal body weight was estimated to be approximately 4 times higher than exposure in humans at recommended therapeutic dose of Paxlovid.

In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9-fold higher than clinical exposures at the authorized human dose of Paxlovid. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6-fold higher than clinical exposures at the authorized human dose of Paxlovid.

Ritonavir

Ritonavir produced no effects on fertility in rats.

Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a

maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Special precautions for storage

Do not store above 25 °C. Do not store in the refrigerator or freeze.

Keep out of the reach of children.

Authorisation number

68793 (Swissmedic).

Packs

Paxlovid: Packs of 30 film-coated tablets, corresponding to 5 daily-doses. [A]

Each 1-day blister card contains 4 nirmatrelvir and 2 ritonavir film-coated tablets.

Marketing authorisation holder

Pfizer AG, Zürich.

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