Date: 14 April 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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: temporary authorisation in accordance with Art. 9a TPA approved on 15.06.2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

3CL(pro)	3C-like protein
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
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
BID	Twice a day
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID	Coronavirus disease 2019
CYP	Cytochrome P450
DDI	Drug-drug interaction
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
FOPH	Federal Office of Public Health
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICU	Intensive care unit
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
mITT	Modified intention-to-treat
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
q12h	Every 12 hours
PBPK	Physiology-based pharmacokinetics
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
RTV	Ritonavir
SAE	Serious adverse event

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SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	Standard of care
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)
VOC	Variant of concern

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance nirmatrelvir of the medicinal product mentioned above.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

Authorisation for a COVID-19 medicinal product
In connection with the COVID-19 pandemic, the applicant requested a rolling submission procedure.

OPEN project EMA
Swissmedic has been participating in the meetings of the EMA's OPEN project. Further information at: *EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu).*

2.2 Indication and Dosage

2.2.1 Requested Indication

Paxlovid is indicated for the treatment of COVID-19 in adults and adolescents aged 12 years and over and weighing at least 40 kg, who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (see section "Clinical Efficacy").

2.2.2 Approved Indication

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults 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 applied standard dosage:

The recommended dosage in adults and adolescents (aged 12 years and over and weighing at least 40 kg) is 300 mg nirmaltrevir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days.

Paxlovid should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days after onset of symptoms. 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.

Paxlovid can be taken with or without food. The tablets should be swallowed whole and not chewed, broken or crushed.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	14 January 2022
Formal control completed	18 January 2022
Rolling submission	25 January to 23 February 2022
Predecision	15 March 2022
Answers to Predecision	25 May 2022
Final Decision	15 June 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Coronavirus disease 2019 (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).

The clinical spectrum of COVID-19 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, up to 20% of patients will present severe (significant lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan dysfunction) that might ultimately lead to death. Patients with risk factors (e.g. old age, obesity, chronic lung, kidney or heart disease, active cancer or immunosuppression, diabetes) are more prone to develop severe disease course and death.

Vaccines have been developed for the prevention of COVID-19. For the treatment of COVID-19, apart from the usual standard-of-care techniques, several drugs have been tested for the management of hospitalised patients throughout the course of the pandemic. Currently available therapeutics in Switzerland, depending on the status of the disease and patient characteristics, are essentially dexamethasone, remdesivir, baricitinib and various monoclonal antibodies. Monoclonal antibodies are in principle used in non-hospitalised patients and the other drugs usually for treating hospitalised patients. Since the efficacy of monoclonal antibodies depends on their ability to bind to the spike protein, it can be reduced against some SARS-CoV-2 variants. Therefore, small molecules with activity against other viral targets will be an important part of the therapeutic arsenal. There is currently no approved oral outpatient treatment in Switzerland to prevent severe COVID-19 outcomes.

Paxlovid is an oral combination therapy consisting of two substances, nirmatrelvir and ritonavir. Nirmatrelvir a new peptidomimetic inhibitor of the SARS-CoV-2 $3CL^{pro}$ (3C-like protein), which is the main protease of the coronavirus. Nirmatrelvir binds to the active site of this protease and forms a covalent interaction (as determined by the co-crystal structure). $3CL^{pro}$ digests the virus pp1a and pp1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription, including RdRp, the helicase and the $3CL^{pro}$ itself. Notably, no close human analogues of the coronavirus $3CL^{pro}$ are known. Ritonavir is also a protease inhibitor but is used here in combination as a strong CYP3A4 inhibitor to enhance exposures of nirmatrelvir throughout the entire dosing interval. Notably, ritonavir is a well-known molecule that has long been used in combination as a protease inhibitor booster in HIV treatments.

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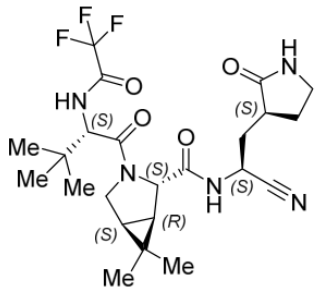
4 Quality Aspects

4.1 Drug Substance

INN: nirmatrelvir
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
Molecular formula: $C_{23}H_{32}F_3N_5O_4$
Molecular mass: 499.54 g/mol
Molecular structure:



PF-07321332

Physico-chemical properties: Nirmatrelvir is a crystalline white to pale-coloured powder. Nirmatrelvir contains six stereogenic centres and is manufactured as a single stereoisomer. The molecule is not ionisable across the aqueous pH range and is non-hygroscopic.

The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specifications: In order to ensure a consistent quality of Ritonavir, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability: The bulk drug substance is packaged in polythene bags. A stability study, carried out according to the current guideline recommendations, was performed. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug Product

Nirmatrelvir 150 mg film-coated tablet

Nirmatrelvir is a 150 mg immediate release film-coated tablet. The dosage form is described as an oval, pink, film-coated tablet with “PFE” debossed on one tablet face and “3CL” debossed on the opposite tablet face.

The 150 mg film-coated tablets are manufactured using a conventional manufacturing process.

Adequate tests and acceptance criteria for release and shelf-life have been established. Analytical methods have been described and validated according to ICH requirements.

Ritonavir 100 mg film-coated tablet

Ritonavir 100 mg is a white to off-white, capsule-shaped, film-coated tablet, debossed with “H” on one side and “R9” on other side.

Adequate tests and acceptance criteria for release and shelf-life have been established for the control of the finished product. Analytical methods have been described and validated according to ICH requirements.

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Co-packed Paxlovid

The container closure system for 2 x nirmatrelvir 150 mg film-coated tablets and 1 x ritonavir 100 mg film-coated tablet consists of a composite oriented polyamide / aluminium foil / polyvinylchloride (OPA/Al/PVC) foil blister with aluminium foil lidding, where each tablet is placed into an individual blister cavity.

Appropriate stability data have been generated for nirmatrelvir 150 mg film-coated tablets in the packaging material intended for commercial use and according to the relevant international guidelines. For the ritonavir 100 mg film-coated tablets appropriate supporting data have been generated in aluminium / aluminium blisters.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Nirmatrelvir is an inhibitor of the main protease of the coronavirus ($3CL^{pro}$), which is indispensable for virus replication and transcription. No close human analogues of $3CL^{pro}$ are known.
The applicant investigated the effect of the combination of nirmatrelvir with ritonavir (inhibitor of the major CYP enzymes responsible for inactivation of nirmatrelvir) only in a few proof-of-concept studies. Therefore, the safety margins given below are a comparison of a nirmatrelvir treatment *in vitro* or *in vivo* with the clinical exposure after treatment with the combination. Some final documents are still outstanding and will be submitted as post-approval commitments.

5.1 Pharmacology

Nirmatrelvir and its major metabolite M4 inhibited SARS-CoV-2 $3CL^{pro}$ with IC_{50} values of 19.2 nM and 17.5 nM (binding constant (K_i) values 3.11 nM and 3.15 nM). Nirmatrelvir was also active against SARS-CoV-2 common variants (i.e. USA-WA1, Alpha, Beta, Lambda, Gamma, Delta, Mu and Omicron) in several susceptible cell lines, with EC_{50} values between 15.9 nM and 217 nM. As nirmatrelvir and M4 are P-glycoprotein (P-gp) substrates, their therapeutic index increased up to 58-fold in the absence of cellular P-gp. Combination of ritonavir with nirmatrelvir resulted in increased antiviral efficacy.

In vitro replication efficacy of recombinant SARS-CoV-2 containing mutations in $3CL^{pro}$ is currently being studied. Nirmatrelvir had no effect (IC_{50} >10 µM) on the activity of several studied mammalian proteases.

Oral administration of nirmatrelvir (up to 1000 mg/kg twice daily) in a mouse-adapted model of coronavirus infection reduced viral titers in the lungs up to 4.2 $\log_{10}$ by Day 3 post-infection. The treatment also significantly improved infection-dependent body weight loss and lung histology.

Secondary pharmacology investigations showed no off-target activities up to 100 µM, i.e. 12-fold total human C_{max} of nirmatrelvir at therapeutic dose (39-fold the predicted human unbound C_{max}). The drug substance caused no adverse effects on respiratory or central nervous system function in rats at exposure levels corresponding to 17-fold human C_{max} at therapeutic dose. Treatments resulting in exposure levels up to approx. 3.6-fold the clinical exposure did not impact cardiovascular system function in monkeys. The outcome of the repeat-dose studies supports this conclusion.

5.2 Pharmacokinetics

Following oral administration of nirmatrelvir, T_{max} was between 0.25 and 1.5 h in rats and approx. 0.25 h in monkeys. Plasma C_{max} and AUC increased almost dose-dependently in rats. The terminal half-life of nirmatrelvir after oral dosing in rats was 2.8-14 h, which is in a comparable range to that in humans administered nirmatrelvir in combination with ritonavir (6.8 to 8 h). Oral bioavailability in rats was dose-dependent, reaching 100% at 1000 mg/kg, whereas bioavailability in humans at therapeutic dosing was estimated to be 55%.

The unbound fraction of nirmatrelvir in plasma was approx. 30% in rats, monkeys and humans, independently of the concentration. In rabbits and dogs, the unbound fraction in plasma increased with increasing dose, reaching up to 80%. Nirmatrelvir did not show preferential distribution into blood cells. The distribution of nirmatrelvir into tissues is currently being studied and the respective report will be submitted as a post-approval commitment.

CYP3A4 was identified as the major metabolising enzyme. Five metabolites were generated via hydroxylation and dehydrogenation *in vitro*. The main metabolite across species was M4 (arising from hydroxylation). Metabolites M5 and M8 were generated *in vivo* by the gut microflora. No human-unique metabolites were observed *in vitro*. *In vivo*, nirmatrelvir was the main circulating drug-related entity in plasma from rats, monkeys and humans following oral administration.

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After administration of nirmatrelvir (up to 1000 mg/kg to rats and 10 mg/kg/day to monkeys), the percentage of dose excreted unchanged was low (rats: 17% in urine and 9-22% in bile/faeces; monkeys: 7% in urine and 4% in faeces). M4 was the most abundant metabolite in excreta. In humans administered nirmatrelvir in combination with ritonavir, nirmatrelvir was the major drug-related material in excreta, with 55.0% in urine and 27.5% in faeces.

5.3 Toxicology

The repeat-dose studies were conducted in rats (up to 1000 mg/kg/day) and cynomolgus monkeys (600 mg/kg/day (300 mg/kg/day twice daily)) using the oral route as intended in the clinical setting. Exposures achieved in animals were several fold higher than those in humans after treatment with nirmatrelvir and ritonavir. The pivotal studies were conducted for up to 1-month with a 2-week recovery phase in both toxicological species. The duration of these studies is in line with the requirements outlined in ICH M3 to support short-term clinical use (not more than 10 days).

Given that ritonavir is a marketed product with a known safety profile, and that the achieved nirmatrelvir exposure in all tests was higher than human exposure levels, the lack of toxicological studies with a combination of nirmatrelvir and ritonavir is acceptable, in line with ICH M3(R2).

No adverse test item-related effects were observed in repeat-dose studies.

Nirmatrelvir was not genotoxic *in vitro* or *in vivo*. Carcinogenicity studies were not conducted, which can be accepted as the treatment duration in humans is limited to 5 days.

Oral nirmatrelvir administration did not affect fertility at doses up to 1000 mg/kg/day in male and female rats, corresponding to an exposure of approximately 4.1 and 4.4-fold the clinical exposure. In embryo-foetal development studies in rats, the NOAEL for both maternal and developmental toxicity was 1000 mg/kg/day, corresponding to 7.8-fold the human AUC_{24} at therapeutic dose. In rabbits, lower mean foetal weight (0.91x control) was observed at 1000 mg/kg/day. The NOAEL for developmental toxicity was 300 mg/kg/day, corresponding to approx. 2.8-fold human AUC_{24} at therapeutic dose. In the pre-and postnatal developmental toxicity study, the high dose of 1000 mg/kg/day was considered the NOAEL for parental F0 systemic toxicity and F1 developmental and systemic toxicity, corresponding to approx. 8-fold the human exposure at therapeutic dose. The Information for healthcare professionals adequately describes reproductive and developmental toxicity findings.

The applicant did not perform juvenile animal studies. The PIP for nirmatrelvir does not require any nonclinical measures.

The environmental risk assessment is in progress; the ERA will be submitted as a post-approval commitment.

The Nonclinical Safety Specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use.

5.4 Nonclinical Conclusions

The submitted documentation is considered appropriate to conduct a risk assessment for nirmatrelvir. The submitted nonclinical data support the approval of Paxlovid in the proposed indication. The relevant information has been included in the Information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption
The administration of a nirmatrelvir suspension plus RTV with a high-fat, high-calorie meal had no relevant impact on nirmatrelvir exposures. The impact of food on the absorption of the nirmatrelvir tablet in combination with RTV was not formally investigated, but nirmatrelvir /RTV was administered independently of food in the pivotal Phase 2/3 study. The median nirmatrelvir tmax after fasted administration of the tablet + RTV was about 3 hours.

Dose proportionality
Nirmatrelvir exposures increased less than dose proportionally after single (150 mg to 1500 mg) and multiple (75 mg to 500 mg BID) dose administration, independently of the co-administration of RTV.

Pharmacokinetics after multiple dosing
Nirmatrelvir reached its steady state on Day 2 after RTV-boosted BID dosing. There was an approximately 2-fold accumulation after 5 or 10 days of RTV-boosted BID dosing.

Distribution
Nirmatrelvir *in vitro* plasma protein binding was about 70% and over the range of 0.3 to 10 µM independent of the Nirmatrelvir concentration. The *in vitro* blood-to-plasma ratio was 0.68, indicating limited penetration of Nirmatrelvir into red blood cells.

After administration of Nirmatrelvir /RTV at 300 mg/100 mg, the mean apparent volume of distribution (Vz/F) of Nirmatrelvir in healthy subjects was 109.4 L. The Nirmatrelvir Vz/F in COVID-19 patients is unknown.

Metabolism & elimination
Nirmatrelvir was metabolised exclusively by CYP3A – mainly CYP3A4 – *in vitro*. In plasma, unchanged NIRMATRELVIR was the main compound after administration of a single 300 mg dose of Nirmatrelvir boosted with 100 mg RTV. Only traces of M4, M5 and M8 were detected. M4 was the major metabolite of Nirmatrelvir formed *in vitro*. Its absence *in vivo* is due to the co-administration of RTV, as the formation of M4 was almost completely inhibited by ketoconazole *in vitro.* The formation of M7 from M5 was mainly catalysed by UGT2B4 with a minor contribution of UGT2.

Unchanged Nirmatrelvir was also the main compound excreted in urine (55% of the normalised dose) and faeces (27.5% of the normalised dose). Additional metabolites detected in urine and/or faeces were M5, M7 and M8. In urine, none of them accounted for more than 3% of the normalised dose. In faeces, M5 was the most abundant metabolite accounting for 11.7% of the normalised dose.

The total recovery of drug-related material plus M8 was 84.9% of the administered Nirmatrelvir dose. After dose normalisation, 58.4% and 41.6% of drug-related material was excreted in urine and faeces, respectively.

After multiple RTV-boosted BID dosing, the Nirmatrelvir half-life was about 8 h. Renal clearance ranged from 2.93 to 3.78 L/h.

Special Populations

Renal function affected Nirmatrelvir PK after co-administration with RTV. The half-life increased from 7.7 h in subjects with normal renal function to 13.4 h in subjects with severe renal impairment (RI). There was a 1.3-fold, 1.4-fold and 1.5- fold increase of Nirmatrelvir Cmax in subjects with mild, moderate or severe RI, respectively. The corresponding increase in Nirmatrelvir AUCinf was 1.24-fold, 1.87-fold and 3.04-fold. There was a linear relationship between Nirmatrelvir CL/F or AUC and eGFR. Simulations of the Nirmatrelvir trough concentrations on Day 5 with a preliminary popPK model supported the proposed dosing recommendations for patients with mild or moderate renal impairment.

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Preliminary data indicated comparable Nirmatrelvir exposures after administration of Nirmatrelvir plus RTV in subjects with moderate hepatic impairment and controls with normal hepatic function.

A final popPK analysis investigating the impact of age, weight and other covariates on Nirmatrelvir exposures is still missing.

Interactions

EFFECT OF OTHER DRUGS ON Nirmatrelvir /RTV

In vitro data

Nirmatrelvir is metabolised by **CYP3A4**. NIRMATRELVIR is a substrate of **P-gp**, but not of NTCP, OATP1B1, OATB1B3, OATP2B1, MATE1, MATE2K, OAT1, OAT3, OCT1, OCT2, PEPT1, OATP4C1 or BRCP

Clinical Data

Perpetrator	**GMR (90% CI)**
Carbamazepin (strong CYP3A4 inducer)	NIRMATRELVIR Cmax: 56.82 (47.04, 68.62) NIRMATRELVIR AUCinf: 44.50 (33.77, 58.65)
	RTV Cmax: 25.59 (18.76, 34.91) RTV AUCinf: 16.57 (13.32, 20.60)
Itraconazole (strong CYP3A4 inhibitor, P-gp inhibitor)	NIRMATRELVIR Cmax: 118.57 (112.50, 124.97) NIRMATRELVIR AUCtau: 138.82 (129.25, 149.11)
	RTV Cmax: 15% ↑ RTV AUCtau: 21% ↑

In the itraconazole interaction study, multiple doses of Nirmatrelvir /RTV were administered, i.e. there was already close to maximum CYP3A4 inhibition due to RTV. Therefore, the further addition of itraconazole had no large effect on Nirmatrelvir exposures.

The dose-normalised Nirmatrelvir AUClast was about 6 to 15-fold higher after boosting Nirmatrelvir with 100 mg RTV.

EFFECT OF NIRMATRELVIR/RTV ON OTHER DRUGS

RTV is a strong inhibitor of **CYP3A4**, an inhibitor of **CYP2D6** and **P-gp** and has also a strong affinity for **CYP2C9**. The known interaction potential of RTV must be considered with regard to the overall interaction potential of the Nirmatrelvir /RTV combination (see Table 1 in the Information for healthcare professionals, section “Interactions”).

In vitro data – Static DDI risk assessment

Direct or time-dependent inhibition of **CYP3A4** cannot be excluded at therapeutic Nirmatrelvir exposures. No interaction potential due to inhibition was identified for CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6.

The induction of **CYP2C8, 2C9, 2C19** and **3A4** at therapeutic Nirmatrelvir exposures cannot be excluded. No induction of CYP2B6 was anticipated.

The inhibition of UGT1A1, 1A4, 1A6, 1A9, 2B7 or 2B15 at therapeutic Nirmatrelvir exposures cannot be completely excluded.

At therapeutic Nirmatrelvir exposures, the inhibition of **P-gp** and **OATP1B1** cannot be excluded. No DDI risk was identified for BCRP, OATP1B3, OCT1, OAT1, OAT3, MATE1 or MATE2K.

Clinical data

Preliminary data indicated no relevant additional effect of Nirmatrelvir /RTV on midazolam (sensitive CYP3A4 substrate) exposures compared to RTV alone.

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6.2 Dose Finding and Dose Recommendation

There was no dose finding study performed. A popPK model was used to evaluate the dose and duration of treatment. The basis of the dosage rationale was as follows: (i) the 300 mg nirmatrelvir regimen was predicted to maintain concentrations above the EC_{90} in most treated participants, (ii) the dose of 100 mg ritonavir was selected as it is already used as a PK enhancer in HIV drugs, (iii) the 5-day duration of the regimen was based on a viral dynamics model of SARS-CoV-2 infection in humans.

6.3 Efficacy

The efficacy of Paxlovid in reducing hospitalisations and deaths due to COVID-19 was assessed in the single pivotal study C4671005 (**EPIC-HR**). It was a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with confirmed SARS-CoV-2 infection, who were at increased risk of progressing to severe illness.

The primary efficacy objective was to compare the efficacy of Paxlovid to placebo for the treatment of COVID-19 in non-hospitalised symptomatic patients with COVID-19 at increased risk of progression to severe disease. The primary efficacy endpoint was the proportion of patients with COVID-19 related hospitalisation or death from any cause through to Day 28. Secondary endpoints included (i) clinical aspects such as time to sustained alleviation or resolution of targeted signs/symptoms, the proportion of participants with all-cause death through to Week 24, the number of COVID-19 medically-related visits and (ii) virological parameters (viral load over time).

The main inclusion criteria were an initial onset of signs/symptoms attributable to COVID-19 with a positive SARS-CoV-2 test (PCR or antigenic) within 5 days prior to randomisation, and at least one characteristic or underlying medical condition associated with an increased risk of developing severe illness. Risk criteria were generally in line with identified risk factors in the scientific literature and the criteria of the FOPH, except for the inclusion of cigarette smoking. A BMI threshold of 25 kg/m^2 as well as an age ≥ 60 years were also considered to be risk factors, which are at the lower bound of the range but acceptable. The main exclusion criteria were prior SARS-CoV-2 infection or vaccination, an oxygen saturation of <92% on room air, moderate or several renal impairment, active liver disease or an anticipated need for hospitalisation within 48 hours after randomisation.

Participants were randomised (1:1) within 48 hours to receive Paxlovid or placebo orally q12h for 5 days. Randomisation was stratified by geographic region and whether participants had received/were expected to receive treatment with COVID-19 therapeutic monoclonal antibodies. Patients were not stratified by time since COVID-19 symptom onset (≤ 3 vs >3 days). This should probably have been performed as the study primary analysis in the mITT population relates to patients who were treated ≤ 3 days after COVID-19 symptom onset. Nevertheless, since time to symptom onset was balanced between treatment arms it likely did not affect the results. Participants were allowed to receive standard-of-care therapy that included corticoids (for any indication, used in 6.2% and 10.5% of the Paxlovid and placebo groups, respectively), monoclonal antibodies (1.1%, 2.3%), favipiravir (2.4%, 3.0%) and remdesivir (0.2%, 1.5%). The slight imbalance in frequency of treatment in the placebo arm is due to the increased number of patients in this group who were hospitalised. The total study duration was up to 24 weeks: study intervention through to Day 5/6, efficacy assessments through to Day 28, a safety follow-up period through to Day 34 and long-term follow-up at Weeks 12 and 24.

An external data monitoring committee reviewed data from a pre-specified 45% interim analysis (Paxlovid n=678, placebo n=683) and confirmed that the criteria for stopping the trial due to efficacy had been achieved. Further enrolment in the study was therefore stopped. Overall, a total of 2396 participants were screened and 2246 participants were randomised, 1120 in the Paxlovid and 1126 in the placebo group. Demographic parameters were well balanced between groups. In the final

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analysis, 51% were male and the median age was 46 years. Only 13% of the study population was aged 65 years or older. 70% of subjects were enrolled in the USA and Europe, which is sufficient to extrapolate to the Swiss population. 62% of the subjects had at least 2 risk factors for severe disease. The most common risk factor at baseline was BMI ≥25 kg/m^2 (80%), followed by hypertension (33%). The applicant considered smoking (39% of subjects) as a risk factor, but the association is controversial in the literature. Still, the proportion of smokers without any other risk factors was low (approx. 9%) and similar between the treatment groups. Risks factors related to immunodeficiency were almost non-existent, representing 0.6% of the study population. Two-thirds of patients had a duration of symptoms ≤ 3 days before treatment. Notably, even though patients with prior known SARS-CoV-2 infection or vaccination were excluded, 51% of the participants were seropositive at baseline.

The proportion of participants who discontinued the treatment phase was low and slightly lower in the Paxlovid (6.0%) vs the placebo (7.7%) group. The primary reason for discontinuation was adverse event (2.1% Paxlovid vs 4.2% placebo). A total of 1053 Paxlovid subjects (94%) and 1039 placebo subjects (92.3%) completed the study. Of these, 78.5% of Paxlovid subjects and 76.8% of placebo arm subjects received 5 days of treatment.

Clinical efficacy was shown to be significant in the final analysis:

- In the mITT analysis set (subjects who received treatment within 3 days of symptom onset and who had not received and were not expected to receive monoclonal antibodies after diagnosis). The rate of COVID-19-related hospitalisation or death from any cause through to Day 29 was of 0.7% (5/697) in the Paxlovid group and 6.5% (44/682) in the placebo group. Statistical significance was met with a $p < 0.0001$. This amounts to an absolute risk reduction of 5.8% and a relative risk reduction of 88.9% for Paxlovid in comparison to placebo. There were 0 deaths in the Paxlovid group and 9 deaths in the placebo group, all related to the disease under study.
- In the mITT1 set (subjects who received treatment within 5 days of symptom onset and who had not received and were not expected to receive monoclonal antibodies after diagnosis). The rate of COVID-19-related hospitalisation or death from any cause through to Day 29 was of 0.8% (8/1039) in the Paxlovid group and 6.3% (66/1046) in the placebo group. Statistical significance was met with a $p < 0.0001$. This amounts to an absolute risk reduction of 5.5% and a relative risk reduction of 87%. There were 0 deaths in the Paxlovid group and 13 deaths in the placebo group, all related to the disease under study.

Clinical efficacy was shown among the majority of pre-specified subgroups and for all comorbidities, except where either few events occurred or a statistical test could not be performed because no participants had the event. As expected, the efficacy of Paxlovid was greater in participants either: aged 65 or older, with high viral load (which might be a predictor of more severe disease), seronegative. On that last aspect, the results in the mITT and mITT1 populations included both seropositive and seronegative patients, with a nearly 50/50 mix. In the mITT1 set, hospitalisation or death from any cause in patients with negative serology was 1.4% in the Paxlovid group (7/487) and 11.5% in the placebo group (58/505), that is an absolute difference of more than 10% ($p < 0.0001$). In patients with positive serology it was 0.19% (1/540) in the Paxlovid group and 1.5% (8/528) in the placebo group. The absolute risk reduction was therefore much lower, at 1.3%, but remained significant ($p = 0.018$). Since it is not reasonably possible to determine serostatus before drug prescription for an oral drug (and a positive serology might not be an absolute marker of protection against the disease, depending on the level of antibodies as well as the changing SARS-CoV-2 variant landscape), this is not considered an issue. The applicant is currently conducting additional studies that should provide more data on treatment benefit in the seropositive population (from vaccination or previous infection).

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Results from various sensitivity analyses were consistent with the primary analysis, including when participants who were lost to follow up before Day 21 were hypothetically assumed to have experienced both COVID-19-related hospitalisation and death.

Other key secondary efficacy analyses indicated that Paxlovid-treated patients stayed fewer days in hospital than those treated with placebo (0.09 vs 0.75 days). In addition, no participants in the Paxlovid group were treated in the ICU. The number of medical visits through to Day 28 was also significantly lower in the Paxlovid group, with a four-fold reduction in comparison to placebo (81 vs 22). In addition, the proportion of participants who achieved sustained alleviation or resolution of all targeted signs and symptoms through to Day 28 was higher in the Paxlovid group (approx. 8%) with median time to resolution also significantly shorter (approx. 2-3 days).

Clinical efficacy correlated with a faster decline in viral load in Paxlovid-treated patients. The initial median baseline viral load was 6.3 $\log_{10}$ cp/ml and 5.9 $\log_{10}$ cp/ml in the mITT and mITT1 populations, respectively. At Day 5, in comparison to placebo, the viral load in the Paxlovid group was 0.90 $\log_{10}$ and 0.74 $\log_{10}$ lower in the mITT and mITT1 sets, respectively ($p < 0.001$). The evolution in viral load was similar between non-immunosuppressed and immunosuppressed patients, but this latter group included very few patients. The applicant mentioned that it is exploring conducting a Phase 2 trial to collect additional virological and efficacy data in immunocompromised patients.

The main SARS-CoV-2 variant during the EPIC-HR study was Delta (>98%), which is congruent with the study period (July 2021-December 2021). Since the target of Paxlovid (3C-like protease) is conserved across all SARS-CoV-2 variants known thus far, Paxlovid is expected to maintain efficacy against the current Omicron variant. This was confirmed by *in vitro* data, with cell-based assays (viability and RT-qPCR viral load measurement) indicating that the EC_{50} values of nirmatrelvir against the original, Alpha, Beta, Delta, Gamma, Lambda, Mu and Omicron variants were similar.

Current work by the applicant is aimed at characterising the potential emergence of nirmatrelvir resistance mutations, typically in samples from patients who experienced treatment failure. *In vitro* assays have indicated that some naturally occurring mutations in the protease (e.g. S144A, Q189K, E166A) are associated with significantly reduced nirmatrelvir activity. Q189K was found in 7 Paxlovid and 7 placebo patients; S144A and E166A occurred once each in Paxlovid-treated patients. As of now, no significant associations were identified between viral baseline protease mutations or treatment-emergent mutations and treatment failure. Overall, surveillance data is very preliminary and active monitoring of treatment-emergent mutations will be of paramount importance.

6.4 Safety

The safety assessment of Paxlovid is primarily based on the final analysis of the pivotal study EPIC-HR at the data cut-off date of 11 December 2021. 2224 participants who received at least one dose of either Paxlovid (n=1109) or placebo (n=1115) were included in the safety analysis set, and 2102 (93.6%) participants had completed the safety follow-up at Day 34. The overall demographic and baseline characteristics of the patients in the safety analysis set were similar in both arms.

The proportion of participants who discontinued the treatment phase was similar between treatment groups (6.0% and 7.7% in the Paxlovid and placebo groups, respectively), and a total of 1053 subjects in the Paxlovid group and 1039 subjects in the placebo group completed the study.
The incidence of adverse events was comparable between groups: 22.6% in the Paxlovid arm and 23.9% in the placebo arm. Most all-cause TEAEs in both treatment groups were mild to moderate (Grade 1 or 2) in severity and essentially related to the COVID-19 disease itself. Grade 3 or 4 TEAEs were less reported in the Paxlovid group (4.1%) than in the placebo group (8.3%). In the Paxlovid group, a total of 34 (3.1%) subjects experienced a Grade 3 AE and 11 (1.0%) had Grade 4 events. The majority of the Grade 3-4 events were reported in the SOCs investigations (creatinine renal clearance decreased, D-dimer increased) and Infections and infestations (COVID-19, COVID-19

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pneumonia, abscess, pyelonephritis, sepsis/viral sepsis). Fewer participants discontinued the treatment phase due to an AE in the Paxlovid group (2.1%) than in the placebo group (4.2%).

Adverse events ≥1% (all grades regardless of causality) that occurred in the Paxlovid group at a greater frequency than in the placebo group were dysgeusia (5.6% vs <1%, respectively), diarrhoea (3.1% vs 2%), hypertension (1% vs <1%), myalgia (1% vs <1%) and vomiting (1.1% vs <1%). These were mostly Grade 1-2. There were 5 (0.4%) cases of Grade 3 TEAEs in the Paxlovid group: 1 case of palpitations, 2 cases of increase in transaminases, 1 case of dysgeusia and 1 case of maculo-papular rash. The AEs leading to drug treatment discontinuation were more frequently reported in the placebo arm than in the Paxlovid arm (4.2% and 2.1%, respectively). The most frequently reported AEs leading to discontinuation with Paxlovid treatment were nausea (0.5%), vomiting (0.4%) and creatinine renal clearance decreased (0.3%).

It is notable that hypertension occurred at a low frequency overall but was more frequent in the Paxlovid group (0.6% vs 0.2% in the placebo group). Of the 7 cases, 6 were low grade and 6 had an event onset between Day 2 and Day 5. One patient had Grade 3 hypertension on Day 5 that did not resolve. The narratives have been reviewed and show that except for 1 SAE of Grade 4 hypertensive crisis (assessed as not related to study intervention by the Investigator in a patient known for chronic arterial hypertension), increases in blood pressure were small. No cases of hypertension were considered as related to Paxlovid by the Sponsor. Due to the limited number of cases, a causal relationship with Paxlovid cannot be concluded at this stage. The applicant has planned to conduct a global safety review of this aspect in its 3 sponsored clinical studies (EPIC-HR, EPIC-SR, EPIC-PEP).

Serious adverse events were reported in a lower proportion of subjects in the Paxlovid group (1.6%) in comparison to the placebo group (6.6%). The SAEs were mostly related to COVID-19, and the most frequently reported were COVID-19 pneumonia, COVID-19 and creatinine renal clearance decreased. These occurred less frequently in the Paxlovid group in comparison to the placebo group (0.5% vs 3.3%, 0.2% vs 0.7% and 0.2% vs 0.3%, respectively).

There were 13 deaths among participants in this study, all of which occurred in the placebo group.

There were no specific laboratory test abnormalities during the first 34 days in the Paxlovid group. No in-depth QTc study was performed, but ECGs collected in the EPIC-HR study were similar between the Paxlovid and placebo groups.

Overall, based on the safety data provided, no major safety concern was identified for Paxlovid. Dysgeusia and diarrhoea were significantly more elevated in the Paxlovid arm, but these were essentially low grade and self-limited. Hypertension events warrants surveillance.
Since subjects with active liver disease or severely impaired kidney function were excluded from the study, no conclusions regarding safety in these groups can be drawn. In addition, the applicant does not recommend Paxlovid during pregnancy or in women of childbearing potential not using adequate contraception.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The main option to prevent severe outcomes in COVID-19 is vaccination. Unvaccinated subjects or patients who did not respond adequately to vaccination are therefore inadequately protected. Currently, various monoclonal antibodies aimed at neutralising SARS-CoV-2 have been developed to prevent a severe course of disease in patients with risk factors. However, depending on the targeted epitope on the Spike protein, their efficacy can be impaired or nullified against some VOCs. Moreover, monoclonal antibodies are intravenous treatments that require complex logistics. There is a need for oral COVID-19 drugs that are simpler to administer and have alternative mechanisms of action.

Beneficial effects and respective uncertainties

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Paxlovid can be administered independently of food. The effect of food on Nirmatrelvir PK in combination with RTV was investigated for a suspension only. No respective PK data are available for the proposed commercial 150 mg tablet, but Paxlovid was administered independently of food in the pivotal efficacy study.

The available data indicate that the addition of Nirmatrelvir does not appear to enhance the interaction potential of ritonavir, i.e. the combination is not worse in that respect than ritonavir alone.

From a pharmacokinetic point of view, no dose adjustments are required for patients with mild or moderate hepatic impairment. The final report of the respective clinical pharmacology study is not yet available.

From a pharmacokinetic point of view, no dose adjustments for patients with mild renal impairment are required.

At least 81% of the patients had observed Nirmatrelvir C12h concentrations ≥ IC90 with the proposed dosing regimen.

In a single pivotal Phase II/III study in non-hospitalised symptomatic adults with COVID-19 at increased risk of progressing to severe illness, Paxlovid significantly reduced the proportion of COVID-19-related hospitalisations or deaths from any cause at Day 28. In the final analysis, results of the primary endpoint (treatment with Paxlovid within 3 days of symptoms, mITT) show a 5.8% absolute reduction in comparison to placebo (6.5% vs 0.7%), that is a relative risk reduction of 88.9%. Results from a key secondary analysis (patients treated within 5 days of symptoms, mITT1) were supportive. Furthermore, no patients died in the Paxlovid treatment group whereas 13 deaths occurred in the placebo group.

Clinical efficacy was shown among all pre-specified subgroups, including (albeit at a reduced rate) in seropositive patients. Vaccinated patients were excluded from the study, and Paxlovid efficacy in this population is as yet unknown. Since immunocompromised patients were essentially not represented in the study, no conclusion can also be drawn for this group. In its response to the preliminary decision, the applicant stated that it will conduct a Phase 2 study to investigate Paxlovid in non-hospitalised immunocompromised symptomatic COVID-19 patients and estimates availability of the clinical study report at the end of 2023.

The EPIC-HR study was performed during the SARS-CoV-2 Delta wave and nearly all patients were infected with this VOC. The efficacy of Paxlovid against the VOC Omicron is not established, but genomic analyses do not indicate potential resistance mutations in its protease gene, and *in vitro* data are reassuring. Monitoring of potential treatment-emergent mutations and activity against potential new variants will be performed by the applicant.

Unfavourable effects and respective uncertainties

The co-administration of ritonavir is necessary to achieve therapeutic Nirmatrelvir exposures. The downside is the substantial but well-known interaction potential of ritonavir. This is appropriately addressed in the Information for healthcare professionals, but a clear layout (e.g. boxed warning) is required, in particular because Paxlovid will be prescribed by healthcare providers possibly not familiar with ritonavir's interactions. Furthermore, the low ritonavir dose and the short treatment duration of 5 days attenuate the DDI risk associated with Paxlovid treatment.

No PK data in subjects with severe hepatic impairment are available.

Dose adjustments for patients with moderate renal impairment are required. Currently, Paxlovid should not be used in patients with severe renal impairment or end stage renal disease.

As a full popPK analysis including the available patient data has not yet been completed, no quantitative information regarding the impact of demographic factors such as age, body weight, and race, etc. on Nirmatrelvir PK is available.

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The effect of Nirmatrelvir on QTc is unknown.

Safety data do not yield major concerns. Overall, adverse events were less frequently reported for Paxlovid than for placebo and the majority were low grade and self-limiting. The incidence of dysgeusia and diarrhoea were significantly increased in the Paxlovid group, but were also of low grade and therefore do not raise concerns regarding premature interruption of treatment by patients. There is a slight concern regarding increased hypertension events, even though most events were low grade. Non-clinical and clinical data do not suggest a risk of QTc prolongation with Paxlovid, but QTc prolongation has not been fully evaluated in humans. There are no data regarding the use of Paxlovid in pregnant women.

Paxlovid is a cytochrome inhibitor, in particular of CYP3A. Therefore, the plasma levels of other drugs metabolised through the cytochrome route can be altered when co-administered with Paxlovid. On the other hand, drugs taken by the patient that are inducers of CYP3A may cause large decreases in Paxlovid levels and alter its efficacy. Assessment of drug-drug interactions is therefore of paramount importance.

Benefit-risk balance

The main concerns from a clinical pharmacology point of view are the potential interactions of Paxlovid, which is addressed in the Information for healthcare professionals. The currently missing data (above all the popPK analysis, including patient data will be submitted as soon as available. The clinical efficacy in the study population and the low safety concern indicates a positive benefit-risk assessment for Paxlovid for the proposed indication.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant 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. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 is temporarily authorized, see «Properties/Effects».

Paxlovid™

Composition

Active substances

PF-07321332 (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

PF-07321332

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, 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

PF-07321332

Film-coated tablet.

1PF-07321332 film-coated tablet contains 150 mg of PF-07321332.

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.

1ritonavir 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 adults 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 PF-07321332 tablets co-packaged with ritonavir tablets.

The daily blister contains two separated parts each containing two tablets of PF-07321332 and one tablet of ritonavir corresponding to the daily administration at the standard dose.

Usual dosage

The recommended dosage is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days.

Paxlovid should be administered as soon as possible after a positive viral test for SARS-CoV-2 (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 hepatic impairment (see «Warnings and Precautions» and «Pharmacokinetics»).

Patients with renal disorders

No dose adjustment is needed in patients with mild renal impairment (eGFR ≥60-<90 ml/min).

In patients with moderate renal impairment (eGFR ≥30-<60 ml/min), the dose of Paxlovid should be reduced to PF-07321332/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid over-exposure (this dose adjustment has not been clinically tested).

Special attention for patients with moderate renal impairment

The daily blister contains two separated parts each containing two tablets of PF-07321332 and one tablet of ritonavir corresponding to the daily administration at the standard dose.

Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of PF-07321332 with the tablet of ritonavir should be taken every 12 hours.

Paxlovid should not be used in patients with severe renal impairment [eGFR <30 ml/min, including patients with End Stage Renal Disease (ESRD) under haemodialysis] (see «Warnings and Precautions» and «Pharmacokinetics»).

Children and adolescents

The safety and efficacy of Paxlovid in patients below 18 years of age have not been established. No data are available.

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.

PF-07321332 must be co-administered with ritonavir. Failure to correctly co-administer PF-07321332 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. 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.

Medicinal products that are potent CYP3A inducers where significantly reduced PF-07321332/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»).

Medicinal products listed below are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated with Paxlovid.

- α_1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene*
- Antianginal: ranolazine
- Anticancer drugs: neratinib, venetoclax, apalutamide
- Antiarrhythmic: amiodarone, bepridil*, dronedarone, encainide*, flecainide*, propafenone*, quinidine*

- Antibiotics: fusidic acid, rifampicin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine
- Antihistamines: astemizole*, terfenadine*
- Antipsychotics/neuroleptics: lurasidone, clozapine, pimozide*, quetiapine
- Ergot derivatives: dihydroergotamine*, ergonovine*, ergotamine, methylergonovine
- GI motility agents: cisapride*
- Herbal products: St. John's wort (*Hypericum perforatum*)
- Lipid-modifying agents:
    - HMG Co-A reductase inhibitors: lovastatin*, simvastatin
    - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide*
- PDE5 inhibitor: avanafil, sildenafil, vardenafil
- Sedative/hypnotics: clorazepate*, diazepam, estazolam*, flurazepam, oral midazolam and triazolam

* not approved in Switzerland

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.

Table 1 lists drugs that are contraindicated or lead to significant interactions when used concomitantly with PF-07321332/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.

Severe renal impairment

No clinical data are available in patients with severe renal impairment (including patients with ESRD). Based on pharmacokinetic data (see «Pharmacokinetics»), the use of Paxlovid in patients with severe renal impairment could lead to over-exposure with potential toxicity. No recommendation in terms of dose adjustment could be elaborated at this stage pending dedicated investigation. Therefore, Paxlovid should not be used in patients with severe renal impairment (eGFR <30 ml/min, including patients with ESRD under haemodialysis).

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 PF-07321332 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

PF-07321332 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.

PF-07321332 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 (PF-07321332/ritonavir) is a CYP3A inhibitor and may increase plasma concentration of drugs metabolized primarily via CYP3A.

Ritonavir is a potent inhibitor of the hepatic enzyme CYP3A4 as well as an inhibitor of CYP2D6 and the drug transporter p-glycoprotein (P-gp). 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 (PF-07321332/ritonavir) is an 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 PF-07321332/ritonavir. Thus, coadministration of PF-07321332/ritonavir 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 1).

PF-07321332 does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 *in vitro* at clinically relevant concentrations. *In vitro* study results showed PF-07321332 may be inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. The clinical relevance is unknown. Based on *in-vitro* data, PF-07321332 has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for PF-07321332 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 1) 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 1 are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated or may interact with PF-07321332/ritonavir and should be used with caution.

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
α1-adrenoreceptor antagonist	↑Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see «Contraindications»).
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.
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, ↑Piroxicam, ↑Propoxyphene*	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities and are therefore contraindicated (see «Contraindications»).
	↑Fentanyl	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 is concomitantly administered with ritonavir.
	↓Methadone (36%, 38%)	Increased methadone dose may be necessary when co-administered with ritonavir dosed as a pharmacokinetic

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		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»).
Antiarrhythmics	↑Amiodarone, ↑Bepridil*, ↑Dronedarone, ↑Encainide*, ↑Flecainide*, ↑Propafenone*, ↑Quinidine*	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine and is therefore contraindicated (see «Contraindications»).
	↑Digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer.
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) 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 PF-07321332/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when co-administered with

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of Paxlovid with apalutamide is therefore contraindicated (see "Contraindications").
	↑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	Serum concentrations of encorafenib 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 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.
	↑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.
	↑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

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		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.
	↑Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The coadministration of vorapaxar with Paxlovid is not recommended (refer to the vorapaxar product information).
	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.
Anticonvulsants	Carbamazepine, Phenobarbital, Phenytoine	Carbamazepine, phenobarbital and phenytoin are strong CYP3A4 inducers, and this may lead to a decreased exposure of PF-07321332 and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine, phenobarbital and phenytoin 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

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		medicines are co-administered with ritonavir. Phenytoin may decrease serum levels of ritonavir.
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, 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

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		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	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.
	↑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%),	

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
	↓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	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of PF-07321332/ritonavir and potential loss of virologic response. Concomitant use of rifampicin with Paxlovid is contraindicated (see «Contraindications»).
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.
Anti-HCV	↑Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and Paxlovid is not

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Antipsychotics	↑Clozapine, ↑Pimozide*	Ritonavir coadministration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see «Contraindications»).
	↑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»).
	↑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-agonist (long acting)	↑Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected. Therefore, concomitant use is not recommended.
Calcium channel antagonist	↑Amlodipine, ↑Diltiazem, ↑Nifedipine	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.
Endothelin antagonists	↑Bosentan	Coadministration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (C_{max}) and AUC.
	↑Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The coadministration of riociguat with Paxlovid is not recommended (refer to riociguat Comprehensive information for professionals).
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»)

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
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 PF-07321332 and ritonavir concomitant use with Paxlovid is contraindicated (see «Contraindications»).
HMG Co-A reductase inhibitors	↑Atorvastatin, ↑Fluvastatin, ↑Lovastatin*, ↑Pravastatin, ↑Rosuvastatin, ↑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»). 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. 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 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.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
Immunosuppressants	↑Cyclosporine ↑Tacrolimus ↑Everolimus	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 cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.
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 (see product information for lomitapide) (see «Contraindications»).
Phosphodiesterase (PDE5) inhibitors	↑Avanafil (13-fold, 2.4-fold)	Concomitant use of avanafil with Paxlovid is contraindicated (see «Contraindications»).
	↑Sildenafil (11-fold, 4-fold)	Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours. Concomitant use of sildenafil with Paxlovid is contraindicated in pulmonary arterial hypertension patients (see «Contraindications»).
	↑Tadalafil (124%, ↔)	The concomitant use of tadalafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions.
	↑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»).
	↑Oral and parenteral midazolam	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

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		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 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»).
	↓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»).
	↑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.
	↑Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.
Sleeping agent	↑Zolpidem (28%, 22%)	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.
Smoke cessation	↓Bupropion (22%, 21%)	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
		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.
Steroids	Inhaled, injectable or intranasal Fluticasone propionate, Budesonide, Triamcinolone	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86%) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g., budesonide and triamcinolone. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.
	↑Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.
	↑Prednisolone (28%, 9%)	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37% and 28% after 4 and 14 days ritonavir, respectively.

Medicinal product class	*Medicinal product within class (AUC change, C_{max} change)*	*Clinical comments*
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.

Abbreviations: ATL=alanine aminotransferase
* not approved in Switzerland

Effects of other medicinal products on pharmacokinetics of Paxlovid

PF-07321332 and ritonavir are CYP3A substrates; therefore, medicinal products that induce CYP3A may decrease PF-07321332 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 PF-07321332 AUC and C_{max} are summarised in Table 2.

Table 2: Interactions with other medicinal products: pharmacokinetic parameters for PF-07321332 in the presence of the co-administered medicinal products

	Dose (schedule)			*Ratio (in combination with co-administered medicinal product/alone) of PF-07321332 pharmacokinetic parameters (90% CI); no effect=100*	
Co-administered medicinal product	*Co-administered medicinal product*	*PF-07321332/ ritonavir*	*N*	*C_{max}*	*AUC[a]*
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg twice daily (5 doses)	9	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}=maximum plasma concentrations.
[a] For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.
[b] 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 no 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 no data from the use of Paxlovid in pregnant women.

There was no PF-07321332-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 (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

There are no data on the use of Paxlovid in breast-feeding women.

It is unknown whether PF-07321332 is present in human or animal milk, and the effects of it on the breast-fed newborn/infant, or on milk production are also unknown. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of 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 and for 7 days after completing Paxlovid.

Fertility

There are no human data on the effect of Paxlovid (PF-07321332 and ritonavir) or ritonavir alone on fertility. Both PF-07321332 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

The safety of Paxlovid is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomised, placebo-controlled trial in non-hospitalised adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection (see «Properties/Effects»). A total of 2224 symptomatic adult participants 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either Paxlovid (PF-07321332/ritonavir 300 mg/100 mg) (n=1109) or placebo (n=1115). Study drugs were to be taken twice daily for up to 5 days.

The most common adverse reactions reported during treatment with Paxlovid (PF-07321332/ritonavir 300 mg/100 mg) every 12 hours for 5 days and during 34 days after the last dose were dysgeusia (5.6%), diarrhoea (3.1%), headache (1.4%) and vomiting (1.1%).

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 3: Adverse reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Immune system disorders	Common	Hypersensitivity
Nervous system disorders	Common	Dysgeusia, headache
Gastrointestinal disorders	Common	Diarrhoea, vomiting

Description of specific adverse reactions and additional information

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

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

J05 (not yet assigned)

Mechanism of action

PF-07321332 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 PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

Antiviral activity

PF-07321332 exhibited antiviral activity against SARS-CoV-2 infection of 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. PF-07321332 had cell culture antiviral activity (with EC_{50} values in the low nanomolar range ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3.3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

Resistance

SARS-CoV-2 resistance assays are ongoing.

Phenotypic assessments were conducted to characterize the impact of naturally occurring SARS-CoV-2 Mpro polymorphisms on the activity of PF-07321332 in a biochemical assay using recombinant Mpro enzyme. The clinical significance of these polymorphisms is unknown, and it is

also unknown if results from the biochemical assay are predictive of antiviral activity in cell culture. The following Mpro amino acid substitutions were associated with reduced PF-07321332 activity (≥3-fold higher K_i values): G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). G15S is present in the Lambda variant, which did not have reduced susceptibility to PF-07321332 (relative to USA-WA1/2020) in cell culture.

In addition, three SARS-CoV-2 Mpro amino acid positions where polymorphisms have not been naturally observed were evaluated by substituting alanine at these positions and assessing their impact on activity in biochemical assays. These Mpro amino acid substitutions were associated with reduced PF-07321332 activity (i.e., higher K_i values): Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). The clinical significance of substitutions at these Mpro positions is unknown.

Cell culture resistance selection studies with PF-07321332 using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions: P15A, T50K, P55L, F126L, T129M, and/or S144A. The presence of the substitutions P55L and S144A in MHV Mpro was associated with reduced PF-07321332 susceptibility (~4- to 5-fold higher EC_{50} values). These positions correspond to E55 and S144 in SARS-CoV-2 Mpro, respectively. E55L alone did not affect PF-07321332 activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A reduced PF-07321332 activity by 91.9-fold (based on K_i value). The clinical relevance of these changes is not known.

Among subjects in clinical trial EPIC-HR with sequence analysis data available at both baseline and a post-dose sample (n=361 PF-07321332/ritonavir-treated, n=402 placebo-treated), the following SARS-CoV-2 Mpro or Mpro cleavage site amino acid changes were detected as treatment-emergent substitutions that were more common in PF-07321332/ritonavir-treated subjects relative to placebo-treated subjects (n=number of PF-07321332/ritonavir-treated subjects with emergent substitution); Mpro substitutions: A7S/T/V (n=3), L30F (n=3), M82I/R (n=3), G109E/R/V (n=3), P132L/S (n=4), C145F/R/Y (n=3), D153H/Y (n=3), E166V (n=3), T196A/K/M/R (n=4), W207L/S/del (n=5), A260D/T/V (n=8), D263E (n=3), A266P/V (n=3), and V297A/F/del (n=3); Mpro ORF1ab cleavage site substitutions: Q5324H/R (n=3), A5328P/S (n=6), and T6449I/P (n=3). None of these substitutions in Mpro gene or cleavage regions occurred in PAXLOVID-treated participants who also experienced hospitalization. Thus, the clinical significance of these substitutions is unknown. In a biochemical assay, the P132H/L/S, A260V, and A266V Mpro substitutions did not reduce PF-07321332 activity (K_i fold-change ≤1, <1, and ~2, respectively). The potential phenotypic effect on PF-07321332 susceptibility for the other substitutions is unknown.

Pharmacodynamics

No information provided.

Clinical efficacy

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 (PF-07321332 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 2246 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 46 years with 13% of participants 65 years of age and older (3% were 75 years of age and older); 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of participants had onset of symptoms ≤3 days from initiation of study treatment; 81% had a BMI $\geq$25 kg/m^2 (37% a BMI $\geq$30 kg/m^2); 12% had diabetes mellitus; less than 1% of the study population had immune deficiency, 47% of participants were serological negative at baseline and 51% were serological positive. The mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/ml (2.87); 26% of participants had a baseline viral load of >10^7 (copies/ml); 6.2% 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 (>98%), mostly clade 21J (based on interim analysis).

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

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (-9.0%, -3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was <0.0001 with 2-sided significance level of 0.002. Table 4 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

Table 4: Efficacy results in non-hospitalised adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 monoclonal antibody treatment at baseline (mITT1 analysis set)

	Paxlovid (N=1039)	**Placebo (N=1046)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%) Reduction relative to placebo[a] [95% CI], %	8 (0.8%) -5.62 (-7.21, -4.03)	66 (6.3%)
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval, N= number of patients.
[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 -5.8% with 95% CI of (-7.8%, -3.8%) in participants dosed within 3 days of symptom onset, and –5.2% with 95% CI of (-7.9%, -2.5%) 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 1379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the Paxlovid group, and 44/682 (6.45%) in the placebo group.

Results from subgroup analyses were consistent with those in the overall population regardless of baseline serology status (Table 5).

Table 5: 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	1039	1046
Serology Negative	n=487	n=505
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI], % p-value	7 (1.4%) 1.47 (0.70, 3.05) -10.25 (-13.28, -7.21) p<0.0001	58 (11.5%) 11.71 (9.18, 14.89)

Serology Positive	n=540	n=528
Patients with hospitalisation or death[a] (%)	1 (0.2%)	8 (1.5%)
Estimated proportion over 28 days [95% CI], %	0.19 (0.03, 1.31)	1.52 (0.76, 3.02)
Reduction relative to placebo [95% CI], %	-1.34 (-2.45, -0.23)	
p-value	p=0.0180	

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.

Temporary authorisation

The medicinal product Paxlovid has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

The pharmacokinetics of PF-07321332/ritonavir have been studied in healthy participants.

Ritonavir is administered with PF-07321332 as a pharmacokinetic enhancer resulting in higher systemic concentrations of PF-07321332.

Upon repeat-dose of PF-07321332/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.

Absorption

Following oral administration of PF-07321332/ritonavir 300 mg/100 mg after a single dose, the geometric mean PF-07321332 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 PF-07321332/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 modestly increased the exposure of PF-07321332 (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of PF-07321332 co-administered with ritonavir tablets.

Distribution

The protein binding of PF-07321332 in human plasma is approximately 69%.
The protein binding of ritonavir in human plasma is approximately 98-99%.

Metabolism

In vitro studies assessing PF-07321332 without concomitant ritonavir suggest that PF-07321332 is primarily metabolised by CYP3A4. Administration of PF-07321332 with ritonavir inhibits the metabolism of PF-07321332. In plasma, the only medicinal product-related entity observed following concomitant administration with ritonavir was unchanged PF-07321332.
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 PF-07321332 when administered with ritonavir was renal excretion of intact medicinal product. Approximately 49.6% and 35.3% of the administered dose of PF-07321332 300 mg was recovered in urine and faeces, respectively. PF-07321332 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 PF-07321332/ritonavir 300 mg/100 mg the arithmetic mean terminal elimination half-life of PF-07321332 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 PF-07321332/ritonavir 300 mg/100 mg the arithmetic mean terminal elimination half-life of ritonavir was 6.1 h.

Kinetics in specific patient groups

The pharmacokinetics of PF-07321332/ritonavir based on age and gender have not been evaluated.

Hepatic impairment

Compared to healthy controls with no hepatic impairment, the PK of PF-07321332 in subjects with moderate hepatic impairment was not significantly different. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of PF-07321332 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.

PF-07321332/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 participants with mild renal impairment were not significantly different. However, in the moderately and severely impaired participants the ratios of the adjusted geometric means (90% CI) for nirmatrelvir AUCinf were 187.40% (148.52%, 236.46%) and 304.49% (237.6%, 390.21%), respectively compared to the healthy control group

Children and adolescents

The pharmacokinetics of PF-07321332/ritonavir in paediatric patients have not been evaluated.

Ethnical origin

Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants.

Preclinical data

No nonclinical safety studies have been conducted with PF-07321332 in combination with ritonavir.

Repeated dose toxicity

Studies of repeated dose toxicity revealed no risk due to PF-07321332.

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 proteinurea 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 PF-07321332.

Genotoxicity studies revealed no risk due to ritonavir.

Carcinogenicity

No carcinogenicity studies have been conducted with PF-07321332.

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

PF-07321332

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 3 times higher than exposure in humans at recommended therapeutic 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 PF-07321332 and 2 ritonavir film-coated tablets.

Marketing authorisation holder

Pfizer AG, Zürich

Date of revision of the text

March 2022.