ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADDRESSED TO MEMBER STATES

FOR UNAUTHORISED PRODUCT

PAXLOVID (PF-07321332 150 mg and ritonavir 100 mg)

AVAILABLE FOR USE

1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for use:** PAXLOVID
- **Active substance(s):** PF-07321332 and ritonavir
- **Pharmaceutical form:** Film-coated tablets
- **Route of administration:** Oral use
- **Strength:** 150 mg PF-07321332, 100 mg ritonavir

2. NAME AND CONTACT DETAILS OF THE COMPANY

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

[Contact details will be added at the National level]

3. TARGET POPULATION

PAXLOVID is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (see section 6).

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

5.1 Posology

PF-07321332 must be coadministered with ritonavir. Failure to correctly coadminister PF-07321332 with ritonavir will result in plasma levels of PF-07321332 that will be insufficient to achieve the desired therapeutic effect.

- **Dosing recommendations and treatment duration**

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 diagnosis of COVID-19 has been made and within 5 days of symptom onset.

- **Specific populations**

Paediatric population

The safety and efficacy of PAXLOVID in paediatric patients younger than 18 years of age have not yet been established. No data are available.

Renal impairment

Mild
No dose adjustment is needed in patients with mild renal impairment.

Moderate
In patients with moderate renal impairment, the dose of PAXLOVID should be reduced to PF-07321332/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid increased toxicity due to over-exposure (this dose adjustment has not been clinically tested).

The daily blister contains two separated parts each containing 2 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**.

Severe
Appropriate dose for patients with severe renal impairment has not yet been determined (see section 6). PAXLOVID is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined (see section 5.2).

Hepatic impairment

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

Severe
No pharmacokinetic or safety data are available regarding the use of PF-07321332 or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, PAXLOVID is contraindicated in patients with severe hepatic impairment (see section 5.2).

- **Method of administration**

For oral use.

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

5.2 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 5.11.

PAXLOVID is contraindicated in patients with severe hepatic impairment.

PAXLOVID is contraindicated in patients with severe renal impairment.

PAXLOVID is contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. PAXLOVID is also contraindicated with 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.

Table 1: Medicinal products that are contraindicated for concomitant use with PAXLOVID

Medicinal product class	Medicinal products within class	Rationale
Concomitant medicinal product levels increased or decreased		
α1-Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 5.4).
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 5.4).

Table 1: Medicinal products that are contraindicated for concomitant use with PAXLOVID

Medicinal product class	Medicinal products within class	Rationale
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity (see section 5.4).
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumour lysis syndrome at the dose initiation and during the dose-titration phase (see section 5.4).
Antiarrhythmics	Amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse reactions from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 5.4).
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antipsychotics/Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 5.4).
	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 5.4).
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
Lipid-modifying agents HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 5.4).
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	Increased plasma concentrations of lomitapide (see section 5.4).

Table 1: Medicinal products that are contraindicated for concomitant use with PAXLOVID

Medicinal product class	Medicinal products within class	Rationale
PDE5 inhibitors	Avanafil	Increased plasma concentrations of avanafil (see section 5.4).
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil associated adverse events (which include hypotension and syncope). See section 5.4 for coadministration of sildenafil in patients with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see section 5.4).
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam	Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenterally administered midazolam, see section 5.4).
PF-07321332/ritonavir level decreased		
Herbal Preparation	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 (see section 5.4).
Anticonvulsant Antiinfective	Carbamazepine[a], Rifampin	Decreased plasma concentration and reduced clinical effects of PF-07321332 and ritonavir.

a. See section 6, Interaction studies conducted with PF-07321332/ritonavir.

5.3 Special warnings and precautions for use

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.

See Table 1 for medicinal products that are contraindicated for concomitant use with PF-07321332/ritonavir (see section 5.2) and Table 2 for potentially significant interactions with other medicinal products (see section 5.4). Potential for interactions should be considered with other medicinal products prior to and during PAXLOVID therapy; concomitant medicinal products should be reviewed during PAXLOVID therapy and the patient should be monitor for the adverse reactions associated with the concomitant medicinal products.

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 coadministered 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

PF-07321332 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PF-07321332 and ritonavir each contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

5.4 Interaction with other medicinal products and other forms of interaction

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 coadministered 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, section 5.2).

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 should be considered only if the benefits outweigh the risks (see Table 2).

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.

Only two drug-drug interaction studies have been performed with PAXLOVID (see the paragraph Interaction studies conducted with PF-07321332/ritonavir in section 6).

The drug-drug interactions listed in Table 1 (section 5.2) and Table 2 correspond to drug-drug interactions related to ritonavir. As a conservative approach they should also apply for PAXLOVID.

Medicinal products listed in Table 1 (section 5.2) and Table 2 are a guide and not considered a comprehensive list of all possible medicinal products that may interact with PF-07321332/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Table 2: 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 section 5.2).
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 coadministered 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 (see section 5.2).
	↑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 coadministered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓Morphine	Morphine levels may be decreased due to induction of glucuronidation by coadministered 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 section 5.2).
Antiarrhythmics	↑amiodarone, ↑dronedarone, ↑flecainide, ↑propafenone, ↑quinidine	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑digoxin	therefore contraindicated (see section 5.2). 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 coadministered 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 Cmax depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with PAXLOVID (refer to the afatinib SmPC). 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 SmPC 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 coadministered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of PAXLOVID with apalutamide is not recommended.
	↑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 SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑Dasatinib, ↑nilotinib, ↑vincristine, ↑vinblastine	Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑Encorafenib	Serum concentrations of encorafenib may be increased when coadministered with ritonavir which may increase the risk of

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		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 SmPC 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 tumour 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 life-threatening potential reactions including hepatotoxicity (see section 5.2).
	↑Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase (see section 5.2 and refer to the venetoclax SmPC). 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 SmPC 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.

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑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 SmPC).
	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 coadministered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is coadministered with ritonavir.
Anticonvulsants	Carbamazepine	Carbamazepine is strong CYP3A4 inducer, and this may lead to a decreased exposure of PF-07321332 and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine with PAXLOVID is contraindicated (see section 5.2).
	↓Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are coadministered 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 section 5.4).
	↑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 coadministered with ritonavir.

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Anti-gout	↑Colchicine	Concentrations of colchicine are expected to increase when coadministered 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 section 5.2).
Antihistamines	↑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 coadministered with ritonavir.
Anti-infectives	↑Fusidic Acid	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 5.2).
	↑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 coadministered with ritonavir as a pharmacokinetic enhancer.
	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 section 5.2).
	↓Voriconazole (39%, 24%)	Coadministration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
	↑Ketoconazole (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 coadministered with ritonavir.
	↑Itraconazole[a], ↑Erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered 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 coadministered 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 section 4.4 and refer to the delamanid Summary of Product Characteristics).
	↑Clarithromycin (77%, 31%), ↓14-OH clarithromycin metabolite (100%, 99%)	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be coadministered 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%.

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	Sulfamethoxazole/Trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
Anti-HIV protease inhibitors	↑Amprenavir (64%, 5-fold)	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the Summary of Product Characteristics for amprenavir.
	↑Atazanavir (86%, 11-fold)	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the Summary of Product Characteristics for atazanavir.
	↑Darunavir (14-fold)	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. For further information, refer to the Summary of Product Characteristics for darunavir.
	↑Fosamprenavir (2.4-fold, 11-fold) measured as amprenavir)	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. For further information, physicians should refer to the Summary of Product Characteristics for fosamprenavir.
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 coadministered 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 Summary of Product Characteristics 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.
Antipsychotics	↑Clozapine, ↑pimozide	Ritonavir coadministration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 5.2).

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑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 section 5.2).
	↑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 section 5.2).
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 area under the curve (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 SmPC).
Ergot Derivatives	↑Dihydroergotamine, ↑Ergonovine, ↑Ergotamine, ↑Methylergonovine	Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 5.2)

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	**Medicinal product within class (AUC change, C_{max} Change)**	**Clinical comments**
HCV Direct Acting Antiviral	↑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 recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
HMG Co-A Reductase	↑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 coadministered 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 section 5.2). 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%)	Due to reductions in ethinyl estradiol concentrations, 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.

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Immunosupressants	↑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 prescribing information for lomitapide) (see section 5.2).
Phosphodiesterase (PDE5) Inhibitors	↑Avanafil (13-fold, 2.4-fold)	Concomitant use of avanafil with PAXLOVID is contraindicated (see section 5.2).
	↑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 section 5.2).
	↑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 section 5.2).
Sedatives/hypnotics	↑Clorazepate, ↑Diazepam, ↑Estazolam, ↑Flurazepam, ↑Oral and parenteral midazolam	Ritonavir coadministration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore contraindicated (see section 5.2). 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

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		midazolam is given orally. Therefore, PAXLOVID should not be coadministered with orally administered midazolam (see section 5.2), 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 coadministered 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 section 5.2)
	↓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 section 5.2).
	↑Alprazolam (2.5-fold, ↔)	Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is coadministered 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 coadministered with careful monitoring for excessive sedative effects.

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Smoke cessation	↓Bupropion (22%, 21%)	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir coadministration.
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

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.
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.

a. See section 6, Interaction studies conducted with PF-07321332/ritonavir.

5.5 Pregnancy and lactation

Women of childbearing potential

There are no human data on the use of PAXLOVID during pregnancy to inform the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment with 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 section 5.4).

Pregnancy

There are no data from the use of PF-07321332 in pregnant women. Animal data with PF-07321332 have shown reproductive toxicity (see section 6).

A large number of pregnant 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. However, animal data with ritonavir have shown reproductive toxicity (see section 6).

PAXLOVID is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There are no human data on the use of PAXLOVID in breast-feeding.

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 the effects 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 the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be interrupted during treatment with PAXLOVID.

Fertility

There are no human data on the effect of PAXLOVID on fertility.

No human data on the effect of PF-07321332 on fertility are available. PF-07321332 produced no effects on fertility in rats (see section 6).

There are no human data on the effect of ritonavir on fertility. Ritonavir produced no effects on fertility in rats.

5.6 Incompatibilities

Not applicable.

5.7 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.

5.8 Shelf life

12 months.

5.9 Storage conditions

Do not refrigerate or freeze. Do not store above 25 °C

5.10 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

5.11 List of excipients

PF-07321332

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

Film coat:
Hydroxy propyl methylcellulose
Titanium dioxide
Polyethylene glycol
Iron oxide red

Ritonavir

Tablet core:
Copovidone
Sorbitan laureate
Silica, colloidal anhydrous
Calcium hydrogen phosphate, anhydrous
Sodium stearyl fumarate

Film coat:
Hypromellose
Titanium dioxide
Macrogol
Hydroxy propyl cellulose
Talc
Silica, colloidal anhydrous
Polysorbate 80

6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile

The most commonly reported 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 (4.8%), diarrhoea (3.9%) and vomiting (1.3%).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); not known (frequency cannot be estimated from the available data).

Table 3a: Adverse reactions with PAXLOVID

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

Adverse reactions with ritonavir

The type, severity and frequency of adverse reactions corresponding to higher dose and use for longer duration in the context of chronic HIV infection listed below might not apply to the use of ritonavir during 5 days in PAXLOVID. Events noted as having a frequency not known were identified via post-marketing surveillance

Table 3b: Adverse reactions with ritonavir

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersensitivity, including urticaria and face oedema.
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common Common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common Common Rare	Pruritus, rash (including erythematous and maculopapular) Acne Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common Common	Arthralgia and back pain Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common Uncommon Not known	Increased urination, renal impairment (e.g., oliguria, elevated creatinine) Acute renal failure Nephrolithiasis
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common	Fatigue including asthenia, flushing, feeling hot
	Common	Fever, weight loss
Investigations	Common Uncommon	Increased amylase, decreased free and total thyroxine Increased glucose, increased magnesium, increased alkaline phosphatase

Description of selected adverse reactions for ritonavir

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridaemia. In some cases, fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

- **Summary of relevant pharmacological properties**

Mechanism of action

PF-07321332 is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of the 3CL protease 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 EC50 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), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 4-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

There is no *in vitro* data available on the antiviral activity against Omicron variant.

Resistance
No information on antiviral resistance is currently available to PF-07321332 with SARS-CoV-2. Studies to evaluate selection of resistance to PF-07321332 with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only *in vitro* resistance selection study with murine hepatitis virus (MHV)-3CL protease is available. It showed a 4.4- to 5-fold decrease in PF-07321332 susceptibility against mutant viruses with 5 mutations (Pro55Leu, Ser144Ala, Thr129Met, Thr50Lys, Pro15Ala) in the MHV-3CL protease following 10 passages in cell culture. The relevance for this to SARS-CoV-2 is not known.

Pharmacodynamic effects

Cardiac electrophysiology
No clinically relevant effect of PF-07321332 on QTcF interval was observed in a double-blind, randomised, placebo-controlled, cross-over study in 10 healthy adults. The model predicted upper bound of 90% confidence interval (CI) for baseline and ritonavir adjusted QTcF estimate was 1.96 ms at approximately 4-fold higher concentration than the mean steady-state peak concentration after a therapeutic dose of PF-07321332/ritonavir 300 mg/100 mg.

Pharmacokinetic properties

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. In healthy participants in the fasted state, the mean half-life ($t_{1/2}$) of a single dose of 150 mg PF-07321332 administered alone was approximately 2 hours compared to 7 hours after administration of a single dose of 250 mg/100 mg PF-07321332/ritonavir thereby supporting a twice-daily administration regimen.

Upon administration of single dose of PF-07321332/ritonavir 250 mg/100 mg as oral suspension formulation to healthy participants in the fasted state, the geometric mean (CV%) maximum concentration (C_{max}) and area under the plasma concentration-time curve from 0 to the time of last measurement (AUC_{last}) was 2.88 ug/mL (25%) and 27.6 ug*hr/mL (13%), respectively. 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 appears to be 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 (CV%) C_{max} and area under the plasma concentration-time curve from 0 to infinity (AUC_{inf}) was 2.21 µg/mL (33) and 23.01 µg*hr/mL (23), respectively. The median (range) time to C_{max} (T_{max}) was 3.00 hrs (1.02-6.00). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (1.8) hours.

Following oral administration of PF-07321332/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV%) C_{max} and AUC_{inf} was 0.36 µg/mL (46) and 3.60 µg*hr/mL (47), respectively. The median (range) time to C_{max} (T_{max}) was 3.98 hrs (1.48-4.20). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (2.2) hours.

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 coadministered 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%.

Biotransformation

In vitro studies assessing PF-07321332 without concomitant ritonavir suggest that PF-07321332 is primarily metabolised by CYP3A4. PF-07321332 does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8 or CYP1A2 *in vitro* at clinically relevant concentrations. PF-07321332 is not an inducer or substrate of other CYP enzymes. Administration of PF-07321332 with ritonavir inhibits the metabolism of PF-07321332. In plasma, the only drug-related entity observed was unchanged PF-07321332. Minor oxidative metabolites were observed in the faeces and urine.

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.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) and other protease HIV inhibitors may influence the pharmacokinetics of ritonavir.

Elimination

The primary route of elimination of PF-07321332 when administered with ritonavir was renal excretion of intact drug. 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. In plasma, the only drug related entity quantifiable was unchanged PF-07321332.

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.

Specific populations

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

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

Patients with renal impairment
Compared to healthy controls with no renal impairment, the C_{max} and AUC of PF-07321332 in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Patients with hepatic impairment
The pharmacokinetics of PF-07321332/ritonavir have not been evaluated in patients with hepatic impairment.

Interaction studies conducted with PF-07321332/ritonavir

CYP3A4 was the major contributor to the oxidative metabolism of PF-07321332, when PF-07321332 was tested alone in human liver microsomes. Ritonavir is an inhibitor of CYP3A and increases plasma concentrations of PF-07321332 and other drugs that are primarily metabolised by CYP3A. Despite being coadministered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of PF-07321332.

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 4 (effect of other medicinal products on PF-07321332).

Table 4: Interactions with other medicinal products: pharmacokinetic parameters for PF-07321332 in the presence of the coadministered medicinal products

Coadministered medicinal product	Dose (schedule)		N	Ratio (in combination with coadministered medicinal product/alone) of PF-07321332 pharmacokinetic parameters (90% CI); no effect=1.00	
	Coadministered medicinal product	PF-07321332/ ritonavir		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}.

Table 4: Interactions with other medicinal products: pharmacokinetic parameters for PF-07321332 in the presence of the coadministered medicinal products

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).

- **Summary of relevant clinical properties**

The efficacy of PAXLOVID is based on the *interim* 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. Preliminary presentation of the final analysis of the primary endpoint has been made available and shows consistent level of efficacy. The study report of the final analysis is awaited.

Eligible participants were 18 years of age and older with at least 1 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. The study excluded individuals with vaccination or a known history of prior COVID-19 infection.

Participants with COVID-19 symptom onset of ≤ 5 days were included in the study.

The primary efficacy endpoint is the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 in the modified intent-to-treat (mITT) analysis set (all treated participants with onset of symptoms ≤ 3 days who had at least one post-baseline visit and did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

Secondary efficacy endpoints included assessments of COVID-19 hospitalisation or death from any cause through Day 28 in the mITT1 analysis set (all treated participants with onset of symptoms ≤ 5 days who had at least one post-baseline visit, and did not receive nor were expected to receive COVID-19 therapeutic mAb treatment). Participants either receiving or expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomisation were excluded from the mITT and mITT1 analyses (8.2%).

A total of 1361 participants were randomised to receive either PAXLOVID or placebo. At baseline, mean age was 45 years with 11.4 % of participants 65 years of age and older (2.9% 75 years of age and older); 52% were male; 63% were White, 5% were Black, 48% were Hispanic or Latino and 20% were Asian; 63% of participants had onset of symptoms ≤ 3 days from initiation of study treatment; 79.4% had a BMI > 25 kg/m2 (36.7% a BMI > 30 kg/m2); 32.4% had hypertension; 12.9% had diabetes mellitus; 55.6% of participants were serological positive at baseline. The mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.78).

Overall, the baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

Table 5: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT analysis set

	PAXLOVID 300 mg/100 mg	**Placebo**
Number of patients (%)	389	385
Patients with hospitalisation or death[a] (%)	3 (0.8%)	27 (7.0%)
Estimated proportion over 28 days [95% CI], %	0.78 (0.25, 2.39)	7.09 (4.92, 10.17)
Reduction relative to placebo [95% CI]* p-value**	-6.32 (-9.04, -3.59) p<0.0001	

*95% two-sided confidence interval *unadjusted* for multiplicity. The 95% two-sided confidence interval *adjusted* for multiplicity for the interim analysis is [-10.61% to -2.02%].
**Two-sided significance level of 0.002.
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, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive

Table 5: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT analysis set

COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset.

a. Covid-19 related hospitalisation or death from any cause.

No deaths were reported in the PAXLOVID group compared with 7 deaths in the placebo group.

mITT1 analyses are considered more representative for the population of interest (initiated within 5 days of symptom onset and dosing recommendation).

Table 6: 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	N=607	N=612
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	6 (1.0%) 1.00 (0.45, 2.21) -5.77 (-7.92, -3.61) p<0.0001	41 (6.7%) 6.76 (5.03, 9.04)
Serology Negative	n=256	n=272
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Difference from placebo [95% CI], % p-value	5 (2.0%) 1.98 (0.83, 4.69) -11.45 (-15.89, -7.02) p<0.0001	36 (13.2%) 13.43 (9.88, 18.13)
Serology Positive	n=344	n=332
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Difference from placebo [95% CI], % p-value	1 (0.3%) 0.29 (0.04, 2.05) -1.22 (-2.66, 0.21) p=0.0947	5 (1.5%) 1.51 (0.63, 3.60)

Abbreviations: CI=confidence interval; mITT1=A modified intent-to-treat analysis set that includes all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, 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.

a. Covid-19 related hospitalisation or death from any cause.

No deaths were reported in the PAXLOVID group compared with 10 deaths in the placebo group.

Table 7: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 patients with treatment initiated > 3 days from symptom onset

	PAXLOVID 300 mg/100 mg	**Placebo**
Number of patients	N=218	N=227
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	3 (1.4%) 1.40 (0.45, 4.29) -4.79 (-8.31, -1.28) 0.0076	14 (6.2%) 6.19 (3.72, 10.24)

Abbreviations: CI=confidence interval; mITT1=A modified intent-to-treat analysis set that includes all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, 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.

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).

- **Preclinical safety data**

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

Toxicology

Repeat-dose toxicity studies up to 1 month duration of PF-07321332 in rats and monkeys resulted in no adverse findings.

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.

Carcinogenesis

PAXLOVID has not been evaluated for the potential to cause carcinogenicity.

PF-07321332 has not been evaluated for the potential to cause carcinogenicity.

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

Genotoxicity

PAXLOVID has not been evaluated for the potential to cause genotoxicity.

PF-07321332 was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human lymphoblastoid TK6 cells and *in vivo* rat micronucleus assays.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Reproductive toxicity

PF-07321332
In a fertility and early embryonic development study, there were no PF-07321332-related effects on fertility and reproductive performance at doses up to 1000 mg/kg/day representing 12x/4.3x based on the predicted human C_{max}/AUC_{24} at a twice-daily dose of 300 mg/100 mg PF-07321332/ritonavir.

The potential embryo-foetal toxicity of PF-07321332 was evaluated in rats and rabbits. There was no PF-07321332-related effect on rat embryo-foetal development up to the highest dose of 1000 mg/kg/day (exposure margin of 16x/7.8x based on total C_{max}/AUC_{24} over the predicted human exposures at a dose of 300 mg/100 mg PF-07321332/ritonavir twice daily). In the rabbit EFD study, adverse PF-07321332-related lower foetal body weights were observed at the highest dose of 1000 mg/kg/day in the presence of nonadverse, low magnitude effects on maternal body weight change and food consumption. These findings were not present at the intermediate dose of 300 mg/kg/day (10x/2.8x C_{max}/AUC_{24} over the predicted clinical exposure).

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.

7. CONDITIONS FOR SAFETY MONITORING

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 adverse reactions. For information on reporting side effects, see section 6.