

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ 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. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Paxlovid 150 mg + 100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink film-coated tablet contains 150 mg of PF-07321332\*.

Each white film-coated tablet contains 100 mg of ritonavir.

\* 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.

### Excipients with known effect

Each pink 150 mg film-coated tablet of PF-07321332 contains 176 mg of lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

### PF-07321332

Film-coated tablet (tablet).

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

### Ritonavir

Film-coated tablet (tablet).

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 side and 'R9' on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (see section 5.1).

### 4.2 Posology and method of administration

#### Posology

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. 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.

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 populations

#### *Renal impairment*

No dose adjustment is needed in patients with mild renal impairment (eGFR  $\geq$  60 to  $<$  90 mL/min). In patients with moderate renal impairment (eGFR  $\geq$  30 to  $<$  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). 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 sections 4.4 and 5.2).

#### **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.

#### *Hepatic impairment*

No dose 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 sections 4.4 and 5.2).

#### *Concomitant therapy with ritonavir- or cobicistat-containing regimen*

No dose adjustment of Paxlovid is needed. Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

#### *Paediatric population*

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

### Method of administration

For oral use.

PF-07321332 must be coadministered with ritonavir. Failure to correctly coadminister 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.

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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 section 4.5).

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

- Alpha<sub>1</sub>-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Anticancer drugs: neratinib, venetoclax
- 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, pimozide, clozapine, 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

#### 4.4 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 and for potentially significant interactions with other medicinal products (see section 4.5). 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 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 section 5.2), 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 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 tablets contain 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 tablets each contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

## **4.5 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).

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.

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.

**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.

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
Alpha <sub>1</sub> -adrenoreceptor antagonist	↑Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see section 4.3).
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 and are therefore contraindicated (see section 4.3).
	↑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

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
		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 4.3).
Antiarrhythmics	↑Amiodarone, ↑Bepridil, ↑Dronedarone, ↑Encainide, ↑Flecainide, ↑Propafenone, ↑Quinidine  ↑Digoxin	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine and is therefore contraindicated (see section 4.3).  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  ↑Abemaciclib  ↑Apalutamide	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 <sub>max</sub> 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.  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 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.

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
	↑Ceritinib	Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with Paxlovid. Refer to the ceritinib 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 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 4.3).
	↑Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir,



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Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
		resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase and is therefore contraindicated (see section 4.3 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	<p>↑Rivaroxaban (153%, 53%)</p> <p>↑Vorapaxar</p> <p>Warfarin,  ↑↓S-Warfarin (9%, 9%),  ↓↔R-Warfarin (33%)</p>	<p>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.</p> <p>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).</p> <p>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.</p>
Anticonvulsants	<p>Carbamazepine,  Phenobarbital,  Phenytoin</p> <p>↓Divalproex,  Lamotrigine,  Phenytoin</p>	<p>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 section 4.3).</p> <p>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.</p>

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
Antidepressants	<p>↑Amitriptyline, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline</p> <p>↑Desipramine (145%, 22%)</p>	<p>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 4.4).</p> <p>The AUC and C<sub>max</sub> of the 2-hydroxy metabolite were decreased 15% and 67%, respectively. Dosage reduction of desipramine is recommended when coadministered with ritonavir.</p>
Anti-gout	↑Colchicine	<p>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 4.3).</p>
Antihistamines	<p>↑Astemizole ↑Terfenadine</p> <p>↑Fexofenadine</p> <p>↑Loratadine</p>	<p>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 section 4.3).</p> <p>Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.</p> <p>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.</p>
Anti-infectives	<p>↑Rifabutin (4-fold, 2.5-fold), ↑25-<i>O</i>-desacetyl rifabutin metabolite (38-fold, 16-fold)</p> <p>↓Voriconazole (39%, 24%)</p>	<p>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.</p>

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
	<p>↑Ketoconazole (3.4-fold, 55%)</p> <p>↑Itraconazole<sup>a</sup>, ↑Erythromycin</p> <p>↓Atovaquone</p> <p>↑Bedaquiline</p> <p>Delamanid</p>	<p>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.</p> <p>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.</p> <p>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 coadministered with ritonavir.</p> <p>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.</p> <p>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).</p> <p>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</p>

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Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
	<p>↑Clarithromycin (77%, 31%), ↓14-OH clarithromycin metabolite (100%, 99%)</p> <p>Sulfamethoxazole/trimethoprim</p> <p>↑Fusidic acid</p> <p>Rifampicin</p>	<p>throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid Summary of Product Characteristics).</p> <p>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%.</p> <p>Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.</p> <p>Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).</p> <p>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 4.3).</p>
Anti-HIV	<p>↑Efavirenz (21%)</p> <p>↑Maraviroc (161%, 28%)</p> <p>↓Raltegravir (16%, 1%)</p>	<p>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.</p> <p>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.</p> <p>Coadministration of ritonavir and raltegravir results in a minor reduction in raltegravir levels</p>

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
	↓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 recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Antipsychotics	↑Clozapine, ↑Pimozide  ↑Haloperidol, ↑Risperidone, ↑Thioridazine  ↑Lurasidone  ↑Quetiapine	<p>Ritonavir coadministration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 4.3).</p> <p>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.</p> <p>Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see section 4.3).</p> <p>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 4.3).</p>
β <sub>2</sub> -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.

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
Endothelin antagonists	↑Bosentan  ↑Riociguat	Coadministration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (C <sub>max</sub> ) and AUC.  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 4.3).
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 section 4.3).
Herbal products	St. John's Wort	Herbal preparations containing St John's wort ( <i>Hypericum perforatum</i> ) due to the risk of decreased plasma concentrations and reduced clinical effects of PF-07321332 and ritonavir and therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
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 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 4.3). 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

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
		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.
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 prescribing information for lomitapide) (see section 4.3).
Phosphodiesterase (PDE5) inhibitors	↑Avanafil (13-fold, 2.4-fold)  ↑Sildenafil (11-fold, 4-fold)  ↑Tadalafil (124%, ↔)  ↑Vardenafil (49-fold, 13-fold)	Concomitant use of avanafil with Paxlovid is contraindicated (see section 4.3).  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 4.3).  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.

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
		Concomitant use of vardenafil with Paxlovid is contraindicated (see section 4.3).
Sedatives/hypnotics	<p>↑Clorazepate, ↑Diazepam, ↑Estazolam, ↑Flurazepam</p> <p>↑Oral and parenteral Midazolam</p> <p>↑Triazolam (&gt; 20-fold, 87%)</p> <p>↓Pethidine (62%, 59%), ↑Norpethidine metabolite (47%, 87%)</p> <p>↑Alprazolam (2.5-fold, ↔)</p>	<p>Ritonavir coadministration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam, and flurazepam and is therefore contraindicated (see section 4.3).</p> <p>Midazolam is extensively metabolised by CYP3A4. Coadministration with Paxlovid may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, Paxlovid should not be coadministered with orally administered midazolam (see section 4.3), 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- to 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.</p> <p>Ritonavir coadministration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3).</p> <p>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 4.3).</p> <p>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</p>



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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
	↑Buspirone	antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.  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.
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 <i>in vitro</i> , 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).

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

Medicinal product class	Medicinal product within class (AUC change, C <sub>max</sub> Change)	Clinical comments
	<p>↑Dexamethasone</p> <p>↑Prednisolone (28%, 9%)</p>	<p>Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.</p> <p>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.</p> <p>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.</p>
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; AUC=area under the curve.

#### Effect of other medicinal products on PF-07321332

Coadministration of multiple oral 200 mg doses of itraconazole increased PF-07321332 AUC<sub>tau</sub> and C<sub>max</sub>. The ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC<sub>tau</sub> and C<sub>max</sub> were 138.82% (129.25%, 149.11%) and 118.57% (112.50%, 124.97%), respectively, when PF-07321332/ritonavir was coadministered with multiple doses of itraconazole as compared to PF-07321332/ritonavir administered alone.

Coadministration of multiple oral 300 mg doses of carbamazepine decreased PF-07321332 AUC<sub>inf</sub> and C<sub>max</sub>. The ratios of the adjusted geometric means for PF-07321332 AUC<sub>inf</sub> and C<sub>max</sub> (90% CI) were 44.50 % (90% CI: 33.77%, 58.65%) and 56.82% (90% CI: 47.04%, 68.62%), respectively, following PF-07321332/ritonavir 300 mg/100 mg coadministration with multiple oral doses of carbamazepine compared to PF-07321332/ritonavir administered alone.

## **4.6 Fertility, pregnancy and 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 as a precautionary measure 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 section 4.5).

### 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 section 5.3).

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 section 5.3).

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

### Breast-feeding

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 the effects on milk production. 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 as a precautionary measure 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 section 5.3).

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

### Summary of the safety profile

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%).

### Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); not known (frequency cannot be estimated from the available data).

**Table 2: Adverse reactions with Paxlovid**

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

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](#).

**4.9 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. PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: {group}, ATC code: 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<sub>50</sub> value of 61.8 nM and EC<sub>90</sub> value of 181 nM) after 3 days of drug exposure. PF-07321332 had cell culture antiviral activity (with EC<sub>50</sub> 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*

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)-Mpro 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-Mpro following 10 passages in cell culture. The relevance for this to SARS-CoV-2 is not known.

## 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 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. Participants with COVID-19 symptom onset of  $\leq 5$  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  $\leq 3$  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  $\leq 5$  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  $\leq 5$  days).

A total of 2,246 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  $\leq 3$  days from initiation of study treatment; 81% had a BMI  $\geq 25$  kg/m<sup>2</sup> (37% a BMI  $\geq 30$  kg/m<sup>2</sup>); 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<sub>10</sub> 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 3 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

**Table 3: 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)**

	<b>Paxlovid (N=1,039)</b>	<b>Placebo (N=1,046)</b>
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%)	8 (0.8%)	66 (6.3%)
Reduction relative to placebo <sup>a</sup> [95% CI], %	-5.62 (-7.21, -4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.

- 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 1,379 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.

**Table 4: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set**

	<b>Paxlovid 300 mg/100 mg</b>	<b>Placebo</b>
Number of patients	N=1,039	N=1,046
Serology Negative	n=487	n=505
Patients with hospitalisation or death <sup>a</sup> (%)	7 (1.4%)	58 (11.5%)
Estimated proportion over 28 days [95% CI], %	1.47 (0.70, 3.05)	11.71 (9.18, 14.89)
Reduction relative to placebo [95% CI]	-10.25 (-13.28, -7.21)	
p-value	p<0.0001	
Serology Positive	n=540	n=528
Patients with hospitalisation or death <sup>a</sup> (%)	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.

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Paxlovid in one or more subsets of the paediatric population in treatment of COVID-19 (see section 4.2 for information on paediatric use).

## **5.2 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.

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  $C_{max}$  and  $AUC_{inf}$  at steady-state was 2.21  $\mu\text{g/mL}$  and 23.01  $\mu\text{g*hr/mL}$ , respectively. The median time to  $C_{max}$  ( $T_{max}$ ) was 3.00 hrs. The arithmetic mean terminal elimination half-life was 6.1 hours.

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  $\mu\text{g/mL}$  and 3.60  $\mu\text{g*hr/mL}$ , respectively. The median time to  $C_{max}$  ( $T_{max}$ ) was 3.98 hrs. The arithmetic mean terminal elimination half-life was 6.1 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 other than CYP3A of which PF-07321332/ritonavir is an inhibitor. Administration of PF-07321332 with ritonavir inhibits the metabolism of PF-07321332. In plasma, the only medicinal product-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 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 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. 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*

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.

### 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.

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.

## **5.3 Preclinical safety data**



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

### PF-07321332

Studies of repeated dose toxicity and genotoxicity revealed no risk due to 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<sub>24</sub>) 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.

No carcinogenicity studies have been conducted with PF-07321332.

### Ritonavir

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

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

Genotoxicity studies revealed no risk due to ritonavir. 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. Ritonavir produced no effects on fertility in rats. Developmental toxicity observed in rats (embryo-lethality, 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 (embryo-lethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### PF-07321332 film-coated tablets

Tablet core:

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Colloidal silicon dioxide

Sodium stearyl fumarate

Film coat:

Hydroxypropyl methylcellulose (E464)

Titanium dioxide (E171)

Polyethylene glycol (E1521)

Iron oxide red (E172)

## Ritonavir film-coated tablets

Tablet core:

Copovidone

Sorbitan laurate

Silica, colloidal anhydrous (E551)

Calcium hydrogen phosphate, anhydrous

Sodium stearyl fumarate

Film coat:

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol (E1521)

Hydroxypropyl cellulose (E463)

Talc (E553b)

Silica, colloidal anhydrous (E551)

Polysorbate 80 (E433)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

1 year.

### **6.4 Special precautions for storage**

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

### **6.5 Nature and contents of container**

OPA/Al/PVC foil blister cards of 30 tablets.

Paxlovid is packaged in cartons containing 5 daily-dose blister cards of 30 tablets.

Each daily blister card contains 4 PF-07321332 tablets and 2 ritonavir tablets for morning and evening dose.

### **6.6 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.

## **7. MARKETING AUTHORISATION HOLDER**

Pfizer Europe MA EEIG

Boulevard de la Plaine 17

1050 Brussels

Belgium

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1625/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

## **A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers responsible for batch release

Pfizer Manufacturing Deutschland GmbH  
Betriebsstätte Freiburg  
Mooswaldallee 1  
79090 Freiburg  
Germany

Pfizer Italia S.r.L  
Localita Marino del tronto  
631000 Ascoli, Piceno  
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<b>Description</b>	<b>Due date</b>
In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply.	30 June 2022
In order to ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established.	30 June 2022
In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided.	30 June 2022
In order to improve the control strategy for the ritonavir film-coated tablets, the limit for dissolution specification of ritonavir film-coated tablets should be tightened according to the results obtained for the biobatches, e.g., to NMT 75% (Q) in 45 min.	30 June 2022

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

PAXLOVID 150 mg + 100 mg film-coated tablets  
PF-07321332 + ritonavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pink film-coated tablet contains 150 mg of PF-07321332  
Each white film-coated tablet contains 100 mg of ritonavir

**3. LIST OF EXCIPIENTS**

Contains lactose.  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 film-coated tablets (20 PF-07321332 tablets + 10 ritonavir tablets)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.  
Scan QR code for product information in the national language.  
URL: <https://pfi.sr/c19oralrx>

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1625/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

paxlovid

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

PAXLOVID  
PF-07321332 150 mg tablet  
ritonavir 100 mg tablet

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Pfizer (logo)

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Paxlovid 150 mg + 100 mg film-coated tablets PF-07321332 + ritonavir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Paxlovid is and what it is used for
2. What you need to know before you take Paxlovid
3. How to take Paxlovid
4. Possible side effects
5. How to store Paxlovid
6. Contents of the pack and other information

#### **1. What Paxlovid is and what it is used for**

Paxlovid contains two active substances PF-07321332 and ritonavir in two different tablets. Paxlovid is an antiviral medicine used for treating adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

COVID-19 is caused by a virus called a coronavirus. Paxlovid stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection, and may prevent you from developing severe illness.

If your symptoms worsen or do not improve after 5 days, talk to your doctor.

#### **2. What you need to know before you take Paxlovid**

##### **Do not take Paxlovid**

- if you are allergic to PF-07321332, ritonavir or any of the other ingredients of Paxlovid (listed in section 6).
- if you are taking any of the following medicines. Taking Paxlovid with these medicines may cause serious or life-threatening side effects or affect how Paxlovid works:
  - Alfuzosin (used to treat symptoms of an enlarged prostate)
  - Pethidine, piroxicam, propoxyphene (used to relieve pain)
  - Ranolazine (used to treat chronic chest pain [angina])
  - Neratinib, venetoclax (used to treat cancer)
  - Amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine (used to treat heart conditions and correct irregular heartbeats)
  - Fusidic acid, rifampicin (used to treat bacterial infections)
  - Carbamazepine, phenobarbital, phenytoin (used to prevent and control seizures)
  - Colchicine (used to treat gout)

- Astemizole, terfenadine (used to treat allergies)
- Lurasidone (used to treat schizophrenia)
- Pimozide, clozapine, quetiapine (used to treat schizophrenia, bipolar disorder, severe depression and abnormal thoughts or feelings)
- Dihydroergotamine and ergotamine (used to treat migraine headaches)
- Ergonovine and methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion)
- Cisapride (used to relieve certain stomach problems)
- St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- Lovastatin, simvastatin, lomitapide (used to lower blood cholesterol)
- Avanafil, vardenafil (used to treat erectile dysfunction [also known as impotence])
- Sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery)
- Clorazepate, diazepam, estazolam, flurazepam, triazolam, midazolam taken orally (used to relieve anxiety and/or trouble sleeping)

## **Warnings and precautions**

### **Liver disease**

Tell your doctor if you have or have had a liver disease. Liver enzyme abnormalities, hepatitis and jaundice have occurred in patients receiving ritonavir.

### **Kidney disease**

Tell your doctor if you have or have had a kidney disease.

### **Risk of HIV-1 resistance development**

If you have untreated or uncontrolled HIV infection, Paxlovid may lead to some HIV medicines not working as well in the future.

### **Children and adolescents**

Do not give Paxlovid to children and adolescents under 18 years because Paxlovid has not been studied in children and adolescents.

### **Other medicines and Paxlovid**

There are other medicines that may not be taken together with Paxlovid. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines:

- medicines used to treat cancer, such as afatinib, abemaciclib, apalutamide, ceritinib, dasatinib, encorafenib, fostamatinib, ibrutinib, nilotinib, vinblastine and vincristine
- medicines used to thin the blood (anticoagulants), such as warfarin, rivaroxaban, vorapaxar
- medicines used to treat convulsions, such as divalproex, lamotrigine
- medicines used for smoking cessation, such as bupropion
- medicines used to treat allergies, such as fexofenadine and loratadine
- medicines used to treat fungal infections (antifungals), such as itraconazole and voriconazole
- medicines used to treat Cushing's syndrome—when the body produces an excess of cortisol—such as ketoconazole tablets
- medicines used to treat HIV infection, such as efavirenz, maraviroc, raltegravir and zidovudine
- medicines used to treat infections (e.g., antibiotics and antimycobacterials), such as atovaquone, fusidic acid, clarithromycin, erythromycin, bedaquiline, rifabutin, delamanid and sulfamethoxazole/trimethoprim
- medicines used to treat mental or mood disorders, such as haloperidol, risperidone and thioridazine
- medicines used to treat high blood pressure in the blood vessels that supply the lungs, such as bosentan and riociguat
- medicines used to treat high blood pressure (hypertension), such as amlodipine, diltiazem and nifedipine

- medicines used to treat heart conditions and correct irregular heartbeats, such as digoxin
- medicines used to treat hepatitis C virus infection, such as glecaprevir/pibrentasvir
- medicines used to lower blood cholesterol, such as atorvastatin, fluvastatin, pravastatin and rosuvastatin
- medicines used to suppress your immune system, such as cyclosporine, tacrolimus and everolimus
- medicines used to treat severe pain, such as morphine, fentanyl, methadone, buprenorphine, norbuprenorphine and other morphine-like medicines
- medicines used as sedatives, hypnotics, and sleeping agent, such as alprazolam, buspirone and zolpidem
- steroids including corticosteroids used to treat inflammation, such as betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, prednisolone, methylprednisolone, mometasone, prednisone and triamcinolone
- medicines used to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease [COPD], such as salmeterol and theophylline
- medicines used to treat depression, such as amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline and desipramine
- medicines used to treat erectile dysfunction (also known as impotence), such as sildenafil and tadalafil
- medicines used as thyroid replacement therapy, such as levothyroxine
- any of the following other specific medicines:
  - oral or patch contraceptive containing ethinyl estradiol used to prevent pregnancy
  - midazolam administered by injection (used for sedation [an awake but very relaxed state of calm or drowsiness during a medical test or procedure] or anaesthesia)

Many medicines interact with Paxlovid. **Keep a list of your medicines to show your doctor and pharmacist.** Do not start taking a new medicine without telling your doctor. Your doctor can tell you if it is safe to take Paxlovid with other medicines.

### **Pregnancy and breast-feeding**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

There is not enough information to be sure that Paxlovid is safe for use in pregnancy. If you are pregnant, it is not recommended to use Paxlovid unless your clinical condition requires this treatment. It is recommended that you refrain from sexual activity or use contraception while taking Paxlovid and for 7 days after completing Paxlovid as a precaution. If you are taking hormonal contraception, as Paxlovid may reduce the effectiveness of this medicine, it is recommended that a condom or other non hormonal method of contraception is used. Your doctor will advise you on the duration of this required adjustment of your contraceptive measures.

There is no information on the use of Paxlovid in breast-feeding. You should not breast-feed your baby while taking Paxlovid and for 7 days after completing Paxlovid as a precaution.

### **Driving and using machines**

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

### **Paxlovid contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

### **Paxlovid contains sodium**

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

### 3. How to take Paxlovid

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Paxlovid consists of 2 medicines: PF-07321332 and ritonavir. The recommended dose is 2 tablets of PF-07321332 (pink tablet) with 1 tablet of ritonavir (white tablet) by mouth twice daily (in the morning and in the evening).

A course of treatment lasts 5 days. For each dose, take all 3 tablets together at the same time.

If you have kidney disease, please talk to your healthcare provider for an appropriate dose of Paxlovid.

Swallow the tablets whole. Do not chew, break or crush the tablets. Paxlovid can be taken with or without meals.

#### **If you take more Paxlovid than you should**

If you take too much Paxlovid, call your healthcare provider or go to the nearest hospital emergency room right away.

#### **If you forget to take Paxlovid**

If you miss a dose of Paxlovid within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of Paxlovid at the same time.

Do not take a double dose to make up for a forgotten dose.

#### **If you stop taking Paxlovid**

Even if you feel better, do not stop taking Paxlovid without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Common:** may affect up to 1 in 10 people

- Altered sense of taste
- Diarrhoea
- Vomiting
- Headache

#### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

### 5. How to store Paxlovid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.



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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Paxlovid contains**

- The active substances in this medicine are PF-07321332 and ritonavir.
  - Each pink film-coated PF-07321332 tablet contains 150 mg of PF-07321332.
  - Each white film-coated ritonavir tablet contains 100 mg of ritonavir.
- The other ingredients in the PF-07321332 tablet are microcrystalline cellulose, lactose monohydrate (see section 2, 'Paxlovid contains lactose'), croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate (see section 2, 'Paxlovid contains sodium'). The film-coating contains hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and iron oxide red.
- The other ingredients in the ritonavir tablet are copovidone, sorbitan laurate, colloidal anhydrous silica, anhydrous calcium hydrogen phosphate, sodium stearyl fumarate. The film-coating contains hypromellose, titanium dioxide, macrogol, hydroxypropyl cellulose, talc, colloidal anhydrous silica and polysorbate 80.

### **What Paxlovid looks like and contents of the pack**

Paxlovid film-coated tablets are available in 5 daily-dose blister cards with a total of 30 tablets packaged in a carton.

Each daily blister card contains 4 PF-07321332 tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening (sun and moon symbols).

PF-07321332 150 mg film-coated tablets are pink, oval-shaped and debossed with 'PFE' on one side and '3CL' on the other side.

Ritonavir 100 mg film-coated tablets are white to off white, capsule shaped, and debossed with 'H' on one side and 'R9' on the other side.

### **Marketing Authorisation Holder**

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

### **Manufacturer**

Pfizer Manufacturing Deutschland GmbH  
Betriebsstätte Freiburg  
Mooswaldallee 1  
79090 Freiburg  
Germany

Pfizer Italia S.r.L  
Localita Marino del Tronto  
631000 Ascoli, Piceno  
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Luxembourg/Luxemburg**  
Pfizer NV/SA  
Tél/Tel: +32 (0)2 554 62 11

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**Österreich**  
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**Polska**  
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**România**  
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**Slovenija**  
Pfizer Luxembourg SARL  
Pfizer, podružnica za svetovanje s področja  
farmacevtske dejavnosti, Ljubljana  
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organizačná zložka  
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**Italia**

Pfizer S.r.l.  
Tel: +39 06 33 18 21

**Sverige**

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**Κύπρος**

Pfizer Ελλάς A.E. (Cyprus Branch)  
Τηλ: +357 22817690

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Pfizer Limited  
Tel: +44 (0) 1304 616161

**Latvija**

Pfizer Luxembourg SARL filiāle Latvijā  
Tel: + 371 670 35 775

**This leaflet was last revised in**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Scan the code with a mobile device to get the package leaflet in different languages.



URL: <https://pfi.sr/c19oralrx>

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

**ANNEX IV**

**CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING  
AUTHORISATION AND PRESENTED BY THE EUROPEAN MEDICINES AGENCY**

**Conclusions presented by the European Medicines Agency on:**

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.