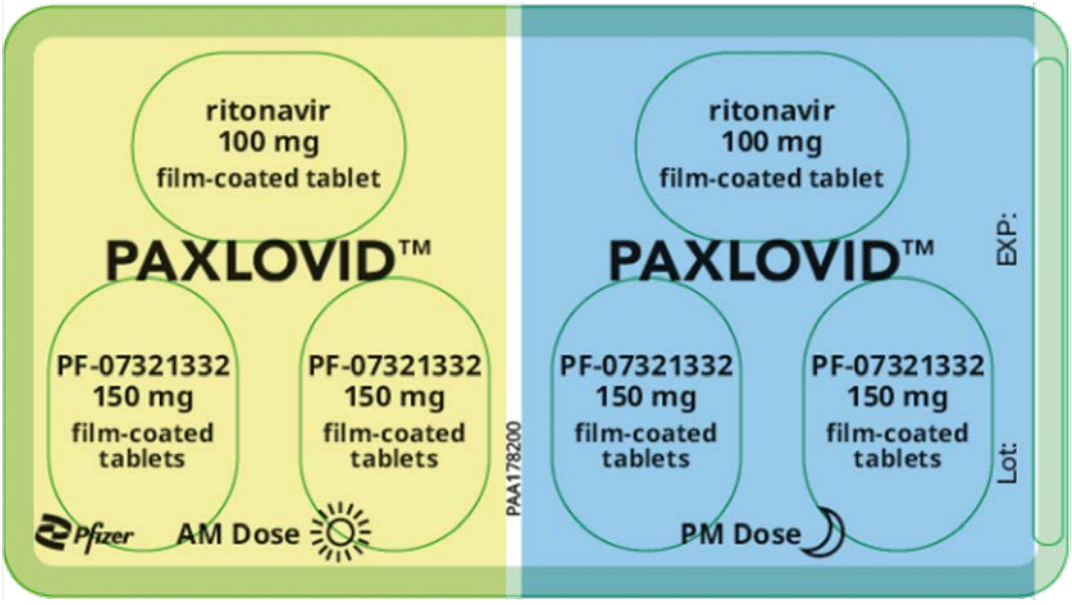
Paxlovid® – Oral antiviral authorised for the treatment of COVID-19

In January of this year, the EMA granted a conditional marketing authorisation (CMA) valid throughout the EU for the oral antiviral medicine Paxlovid® 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.

Paxlovid® contains two active substances, PF-07321332 and ritonavir, in two different tablets.

PF-07321332, a new active substance, is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro). 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. Ritonavir as an active substance has been authorised in the EU since 1986 originally as an antiviral treatment for HIV. Nowadays, it is exclusively used as a PK (pharmacokinetic) enhancer (mostly at 100mg twice daily) for protease inhibitors in HIV and HCV infection; in the context of such PK enhancement use, ritonavir is often referred to as a 'booster'.



The recommended dosage of Paxlovid® is 300 mg of PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), every 12 hours for five days.

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

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

Failure to correctly co-administer PF-07321332 with ritonavir will result in plasma levels of this active substance that will be insufficient to achieve the desired therapeutic effect.

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

Drug-drug interactions

Ritonavir is a well-known inhibitor of CYP3A which may interact with other medicines leading to clinically significant reactions, including potentially life-threatening or fatal reactions, loss of therapeutic effect of Paxlovid® and possible development of viral resistance.

There is a long list of contraindications listed in the SPC for Paxlovid® as follows:

- 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 a CYP3A inducer.

The medicines listed below are stated in the SPC to be a guide and not to be considered a comprehensive list of all possible medicinal products that are contraindicated with Paxlovid®:

- Alpha$_1$-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:
  - HMGCo-A reductase inhibitors: lovastatin, simvastatin
  - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide
- PDES inhibitor: avanafil, sildenafil, vardenafil
- Sedative/hypnotics: clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam

Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid® respectively. These interactions may lead to:

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

Table 1 in the SPC for Paxlovid® includes medicinal products that are contraindicated for concomitant use with PF-07321332/ritonavir and for potentially significant interactions with other medicinal products, along with a clinical comment describing the potential risk of the interaction.

The SPC states that the 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.

The University of Liverpool has an online free access drug interaction checker which includes Paxlovid® drug interactions https://www.covid19-druginteractions.org/

Use in women of childbearing potential, in pregnancy and lactation

There is 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 seven days after completing Paxlovid.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives therefore, patients should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and for one menstrual cycle after stopping Paxlovid.

Paxlovid is not recommended during pregnancy unless the patients clinical condition requires treatment. Breast-feeding should be discontinued during treatment and as a precautionary measure for seven days after completing Paxlovid.

Adverse reactions

The most common adverse reactions reported during treatment with Paxlovid every 12 hours for five days were dysgeusia (5.6%), diarrhoea (3.1%), headache (1.4%) and vomiting (1.1%). This medicinal product is subject to additional monitoring (black triangle). This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

The EMA have advised that community pharmacists be aware of the warnings and advice included in the SPC for this product in particular:

- Which medicines including the herbal product St. John's wort, that are contraindicated with Paxlovid®;
- The company has provided a drug interaction tool on its website which can be accessed through a QR code included in the package leaflet and on the outer carton, https://pfi.sr/c19oralrx;
- The need to review concomitant medicines before and during treatment with Paxlovid®; and
- The need to monitor patients for the adverse reactions associated with any concomitant medicine.

The HSE have not yet clarified the information around patient eligibility or supply of Paxlovid® in primary care.

Further information on Paxlovid® can be found on the EMA website: https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid