PAXLOVID Manufacturing Fact Sheet

PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) is currently authorized for conditional or emergency use in more than 60 countries across the globe.

Early in 2021, our teams at Pfizer started preparing our supply chain and manufacturing nirmatrelvir for PAXLOVID in anticipation of a potential regulatory authorization. Thanks to our at-risk preparation, we had thousands of PAXLOVID courses ready to be shipped within 24 hours of authorization.

What allowed us to scale up our manufacturing so quickly?

- A global supply chain of top-of-the-line facilities
- Longstanding relationships with trusted partners
- Full-scale support for our workforce as they quickly sourced specialized materials and machinery
- A deep heritage in developing oral treatments, with 24 billion pills produced each year
- Applied learnings from the rapid manufacture of the Pfizer-BioNTech COVID-19 vaccine

Our supply chain continues to evolve as more sites come on board – it currently spans 20 supply nodes across more than 10 countries. Since production began, several of Pfizer's key sites have been leveraged. We expect more sites to join as we work to support the manufacture of up to 120 million treatment courses in 2022, pending global demand.

May 2022

How Pfizer Is Preparing Manufacturing for the Next Phase in Fighting Against COVID-19: PAXLOVID

Pfizer began with a significant at risk investment to ensure treatment could be made available to patients, pending clinical success and regulatory authorization or approval.

To achieve this, Pfizer is leveraging four of its key manufacturing locations in Europe and its extensive supplier network to help meet the demand for PAXLOVID.

Ringaskiddy, Ireland

Active Pharmaceutical Ingredient (API) Manufacturer for Nirmatrelvir

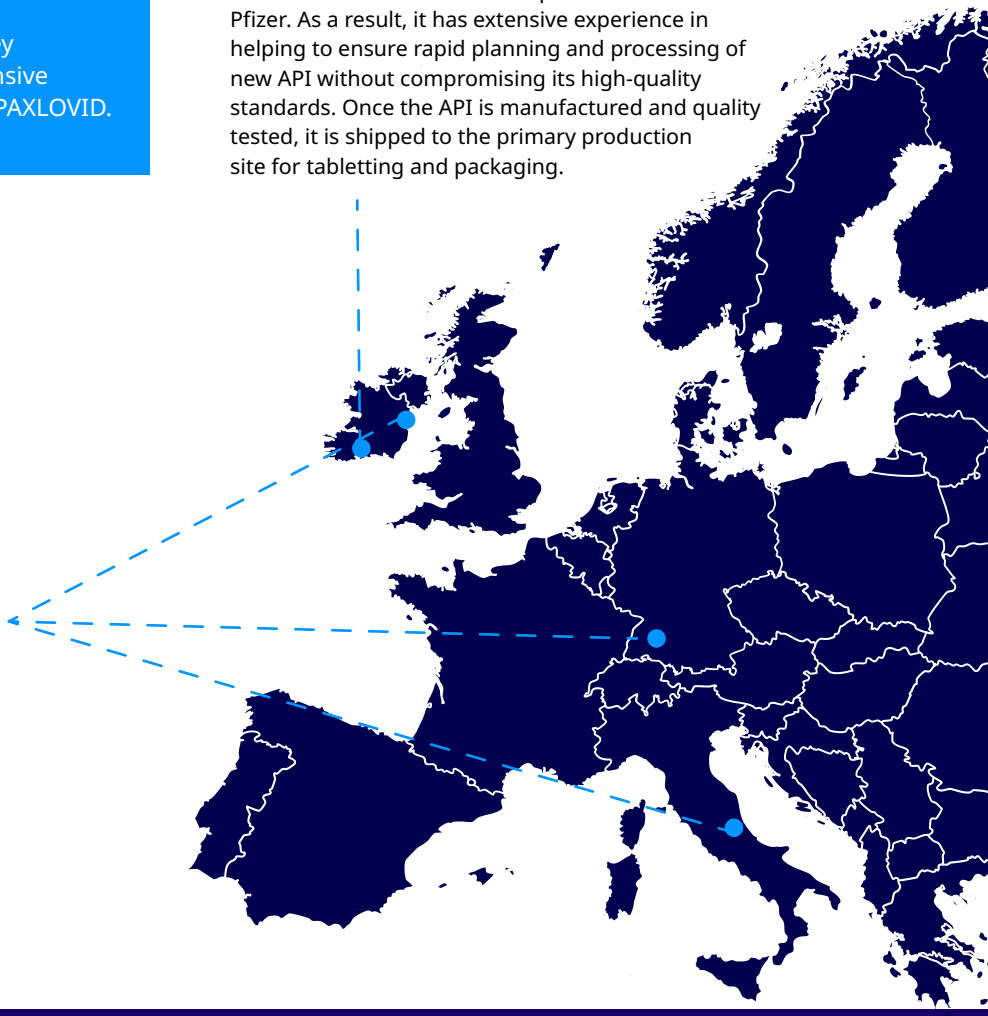
The Ringaskiddy site will manufacture the active pharmaceutical ingredient (API) for nirmatrelvir for PAXLOVID. The site has been involved in the extensive research and development process since work first began on PAXLOVID, including co-developing the API manufacturing process and scaling manufacturing. In addition, Ringaskiddy is the default API manufacturing site for all new small molecule product launches at Pfizer. As a result, it has extensive experience in helping to ensure rapid planning and processing of new API without compromising its high-quality standards. Once the API is manufactured and quality tested, it is shipped to the primary production site for tabletting and packaging.

Freiburg, Germany, Newbridge, Ireland, & Ascoli, Italy

Drug Product Manufacturing, Tabletting and Packaging for Nirmatrelvir

Pfizer selected these sites for their technical knowledge and specialized high-volume manufacturing equipment. They are the primary manufacturing sites for PAXLOVID. Upon receipt and approval of the API, Freiburg, Newbridge and Ascoli begin the production process by mixing, granulating, compressing and coating the tablets, optimizing the entire manufacturing process for the fastest and safest delivery of this treatment. Tablets then quickly progress to packaging on site to meet the high demands for this critical treatment. Their team of quality experts ensure quality standards are adhered to during all stages of manufacturing and packaging of the product.

These facilities have specialized, high-complexity packaging lines to package this treatment on a large scale.



Tackling the pandemic on all fronts – meeting the need for a COVID-19 treatment

Since the start of the pandemic, Pfizer has committed to delivering both treatments and preventative solutions to address COVID-19.

We're confident that PAXLOVID may help reduce illness severity, hospitalization rates, and deaths among a broad population of patients worldwide, pending success from clinical trials.

At Pfizer, we are applying our deep heritage in developing breakthrough therapies and the success from developing and scaling up our manufacturing for the Pfizer-BioNTech COVID-19 vaccine to respond to this global pandemic.

Emergency Use Authorization Statement (EUA)

PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death.

The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

May 2022

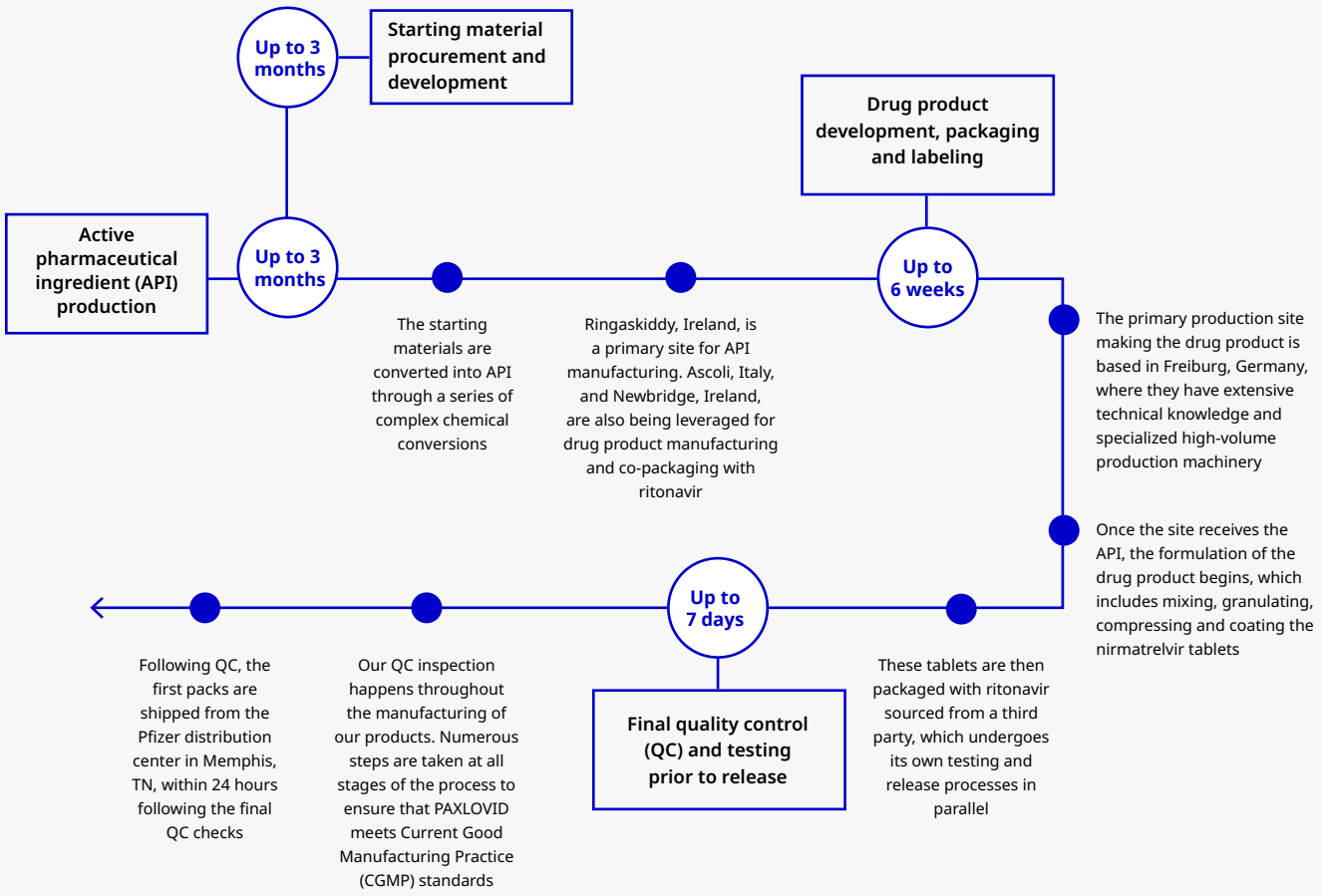
Pfizer

PAXLOVID Supply Journey

Prior to receiving an EUA for PAXLOVID, Pfizer packed and delivered the first shipments from a primarily European-based supply chain.

Producing PAXLOVID (nirmatrelvir) requires large-scale manufacturing capacity across all steps of the production process.

The number of steps involved in the manufacturing of nirmatrelvir for PAXLOVID drives a relatively long lead-time of up to nine months. **However, we have been working quickly to optimize this and are already at an average of around seven months end-to-end.**



At Pfizer, we are constantly looking to improve our processes, shorten timelines and enhance the supply chain to meet the evolving healthcare needs of people around the world.

To learn more about PAXLOVID visit Pfizer.com

May 2022

IMPORTANT SAFETY INFORMATION

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions (eg, toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is **contraindicated with drugs that are highly dependent on CYP3A** for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID is **contraindicated with drugs that are potent CYP3A inducers** where significantly reduced nirmatrelvir or 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 medications due to the delayed offset of the recently discontinued CYP3A inducer:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal Products: St. John's Wort (hypericum perforatum)

There are limited clinical data available for PAXLOVID. **Serious and unexpected adverse events may occur** that have not been previously reported with PAXLOVID use.

Risk of Serious Adverse Reactions Due to Drug Interactions: Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications 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 medications
- Clinically significant adverse reactions from greater exposures of PAXLOVID
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance

Consult Table 1 of the Fact Sheet for Healthcare Providers for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

Hypersensitivity reactions have been reported with PAXLOVID including urticaria, angioedema, dyspnea, mild skin eruptions, and pruritus. Cases of anaphylaxis, TEN, and Stevens-Johnson syndrome have also been reported with components of PAXLOVID (refer to NORVIR labeling). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

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.**

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

Adverse events in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

The following adverse reactions have been identified during post-authorization use of PAXLOVID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions

Required Reporting for Serious Adverse Events and Medication Errors: The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness of the event.

Submit adverse event and medication error reports to FDA MedWatch using one of the following methods:

Online: https://www.fda.gov/medwatch/report.htm

Complete and submit a postage-paid FDA Form 3500 and returning by mail/fax

Call 1-800-FDA-1088 **to request a reporting form**

In addition, please provide a copy of all FDA MedWatch forms to: http://www.pfizersafetyreporting.com/ or by fax (1-866-635-8337) or phone (1-800-438-1985).

PAXLOVID is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.

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

Pregnancy: There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy.

Lactation: There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Contraception: Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

Pediatrics: PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR.

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment. No dosage adjustment is needed in patients with mild renal impairment. **In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of PAXLOVID** to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Providers should counsel patients about renal dosing instructions. **PAXLOVID is not recommended in patients with severe renal impairment** (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, **PAXLOVID is not recommended for use in patients with severe hepatic impairment.**

May 2022