POST-EXPOSURE PROPHYLAXIS PROTOCOL FOR PREVENTING THE SPREAD OF COVID-19 IN CONGREGATE LIVING

BACKGROUND

COVID-19, a viral infection caused by SARS-CoV-2, imposes substantial burden to healthcare systems and significant threat to older adults and other high-risk populations, particularly those in long-term care (LTC) and other congregate living environments. Advanced age and comorbidities increase the risk of infection and severe outcomes, and even periodic waves can lead to rapid transmission, functional decline, hospitalization, and death. COVID-19 outbreaks also disrupt LTC facility operations, including rehabilitation therapy, care coordination, staffing, activities, and visitation. Despite advances in COVID-19 vaccination and treatment, many high-risk individuals remain vulnerable to severe disease due to factors such as chronic conditions, immunosenescence, and reduced vaccine responsiveness. Survivors of COVID-19 are also at risk of long-term sequelae. Implementation of post-exposure prophylaxis (PEP) may play an important role in reducing the transmission and outcomes of COVID-19 infection.

Fast facts:

- One in every six COVID-19-related hospitalizations are in LTC facility residents
- The mortality rate for facility-associated COVID-19 was 4.6 times higher than individuals living in the community
- The Centers for Disease Control and Prevention (CDC) estimates that 81% of COVID-19 deaths happen among people who are 65 and older

IDENTIFICATION AND SCREENING

Following notification of a confirmed COVID-19 case in LTC and other congregate living environments, exposed residents and staff should be identified promptly to facilitate rapid implementation of infection prevention and control measures and consideration of post-exposure prophylaxis (PEP). Early identification is essential because ensitrelvir (Xocova®) for PEP should be initiated within 72 hours of exposure.

1. Identify residents and staff with potential exposure to an individual with confirmed COVID-19.
2. Document:
   - Date and time of exposure
   - Source of exposure
   - Duration and location of exposure
   - Presence of symptoms
3. Assess:
   - Current COVID-19 testing status
   - Risk factors for progression to severe disease
   - Current medications for potential drug interactions
   - Eligibility for PEP
4. Notify the prescribing clinician immediately if an exposed individual may qualify for PEP.

EXPOSURE

Exposure should be assessed using current CDC guidance and facility infection prevention and control policies. Individuals with COVID-19 may transmit SARS-CoV-2 while symptomatic, presymptomatic, or asymptomatic.

EXPOSURE ASSESSMENT

1. Consider an individual exposed if they had close contact with a person with confirmed COVID-19 during that person's infectious period.
2. Evaluate the following exposure characteristics:
   - Close contact exposure, including being within approximately six feet for a cumulative ≥15 minutes over a 24-hour period, while considering additional factors that influence transmission risk, including duration of exposure, ventilation, source control, and use of personal protective equipment.
   - Direct physical contact with an infected individual or contact with infectious secretions.
   - Exposure during aerosol-generating procedures.
   - Exposure in poorly ventilated indoor settings.
   - Repeated close contact in congregate living environments.
3. The infectious period begins 48 hours before symptom onset (or before a positive test in asymptomatic individuals) and continues until CDC criteria for discontinuation of isolation are met.
4. Use clinical judgment when evaluating exposures in LTC and other congregate living environments, particularly for immunocompromised or other high-risk residents.

INITIATION OF POST-EXPOSURE PROPHYLAXIS

1. Begin ensitrelvir (Xocova®) as soon as possible after a qualifying exposure.
2. Therapy should begin within 72 hours following contact with an individual who has COVID-19 according to the Food and Drug Administration (FDA)-approved prescribing information.
3. LTC and other congregate living environments should establish procedures that allow:
   - Rapid exposure reporting
   - Timely provider evaluation
   - Medication procurement
   - Prompt administration of the first dose
4. The efficacy of ensitrelvir (Xocova®) for PEP has been evaluated only when initiated within 72 hours of exposure; initiating therapy beyond this window may reduce potential benefit.
5. Post-exposure parenteral monoclonal antibody therapies are no longer authorized for use in the United States.

SIGNIFICANCE OF COVID-19 INCIDENCE REDUCTION

- SCORPIO-PEP (Stopping Covid-19 Progression with Early Protease Inhibitor Treatment for Post-Exposure Prophylaxis) trial showed significant reductions in the relative risk of COVID-19 among household contacts
  - **67% reduction** in modified intention-to-treat population
  - **57% reduction** in intention-to-treat population
  - **76% reduction** in participants with risk factor for severe illness present
- Household contact with risk factors:
  - 2.4% developed COVID-19 (ensitrelvir (Xocova®) group) compared to 9.9% in placebo group (number needed to treat (NNT) = 13) (relative risk reduction (RRR) = 75.8%)
- Protective efficacy higher than other trials looking at other COVID-19 treatment options.

RISK FACTORS ASSOCIATED WITH CONTRACTING COVID-19	
Health Conditions	*Medication Therapies*
Age ≥ 65 years	Corticosteroids, including:
Cardiovascular Disease	• Prednisone
Chronic Lung Disease (COPD, Asthma)	• Dexamethasone
Chronic Kidney Disease	• Hydrocortisone
Chronic Liver Disease	Chemotherapy agents, including:
Down Syndrome	• Anthracycline derivatives (e.g. doxorubicin)
Sickle Cell Disease	Immunotherapy (e.g. biologic agents)
Dementia	• CAR-T Therapy
Diabetes mellitus	• B-cell depleting therapies (e.g. rituximab)
Smoking	• Abatacept
Stroke and Cerebrovascular Disease	• Anti-IL-agent (e.g. tocilizumab, ustekinumab, guselkumab)
Obesity	Targeted Therapies
Parkinson's Disease	• Tyrosine kinase inhibitors (e.g. ibrutinib)
Tuberculosis	
Mental Health Conditions	
Pregnancy	
Physical Inactivity	
Immunocompromising Conditions:	
• HIV	
• Solid Organ Transplant	
• Hematologic malignancies	

The intention-to-treat population included enrolled household contacts who were at least 12 years of age, had a negative local SARS-CoV-2 test as described above, and were enrolled within 72 hours after symptom onset in the index patient.

The modified intention-to-treat population included all the participants who had undergone randomization, had a central laboratory– confirmed, negative RT-PCR test for SARS-CoV-2 at baseline, and received at least one dose of ensitrelvir or placebo.

Approximately 37% of participants had a risk factor for severe illness.

DOSING

For individuals 12 years of age and older give 375 mg (three 125-mg tablets taken at the same time) orally on Day 1 and 125 mg (one 125-mg tablet) orally on Days 2 to 5

There are no dose adjustments for age, kidney or liver impairment.



ADMINISTRATION

- Should be administered as soon as possible within 72 hours following contact with an individual who has COVID-19
- Take all doses at the same time daily
- Take with or without food
- If a dose is missed, take the missed dose as soon as possible, then take the next dose as scheduled the next day
- For participants requiring enteral administration (via NG or OG tube), ensitrelvir (Xocova®) tablets must be dispersed in either 100% apple juice or whole cow's milk. [14] Ensitrelvir (Xocova®) is practically insoluble in water. [14] The preparation requires gently agitating the mixture for 3 minutes to ensure proper dispersion.[14] The resulting dispersion may be stored at room temperature for up to 3 hours prior to administration, followed by an additional volume flush to clear the tube.[14]

DRUG-DRUG INTERACTIONS

Ensitrelvir (Xocova®) is a strong CYP3A inhibitor and an inhibitor of P-gp and BCRP. In patients taking medications metabolized by CYP3A or transported by P-gp or BCRP, ensitrelvir (Xocova®) may increase plasma concentrations of those medications and may potentially lead to severe, life-threatening, or fatal events from increased exposure of concomitant medications. In addition, medications that induce CYP3A may decrease concentrations of ensitrelvir (Xocova®), leading to loss of therapeutic effect of ensitrelvir (Xocova®).

The ensitrelvir (Xocova®) package insert lists the following drugs as contraindicated with ensitrelvir (Xocova®): quinidine, apalutamide, enzalutamide, carbamazepine, phenytoin, colchicine, rifampin, lurasidone, pimozide, eplerenone, ivabradine, lumacaftor/ivacaftor, dihydroergotamine, ergotamine, methylergonovine, St. John's wort, simvastatin, voclosporin, lomitapide, finerenone, triazolam.

This list is provided as a guide and is not a comprehensive list of all possible drugs that may interact with ensitrelvir (Xocova®).

Prior to prescribing ensitrelvir (Xocova®), review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.

The website www.covid19-druginteractions.org/checker may be a useful tool to screen for drug-drug interactions by entering ensitrelvir (Xocova®) as the COVID-19 drug and then any co-medications to check for interactions.

ADVERSE EFFECTS AND MONITORING

- Headache, diarrhea, cough
- Other adverse effects: fatigue, respiratory, thoracic, or mediastinal disorder
- Allergic reactions, including severe allergic reactions (anaphylaxis)

Laboratory Abnormalities: Asymptomatic hemoglobin declines from baseline of >2 g/dL

Monitoring: There are no specific monitoring recommendations for use of ensitrelvir (Xocova®); however, clinicians should monitor for CYP3A drug interactions and concurrent medication usage.

DURATION OF PROTECTION AND PHARMACOKINETICS

1. Ensitrelvir (Xocova®) is administered as a single 5-day course for post-exposure prophylaxis.
2. Pharmacokinetic studies indicate that ensitrelvir (Xocova®) has an apparent terminal elimination half-life of approximately 42–48 hours. Drug concentrations may remain detectable for approximately 9–10 days following completion of therapy; however, the duration of clinical protection has not been established.
3. Repeat courses for subsequent COVID-19 exposures have not been evaluated, and there are currently no recommendations regarding repeat post-exposure prophylaxis.

Ensitrelvir (Xocova®) is not a substitute for COVID-19 vaccination. Individuals should continue to receive recommended COVID-19 vaccination and follow infection prevention and control measures according to current public health guidance.

COST & BARRIERS TO IMPLEMENTATION

COVID-19 continues to pose a high economic burden as a result of direct and indirect costs, with the greatest healthcare resource utilization, including hospitalizations, reported in individuals at high risk of progressing to severe COVID-19.

Congregate care facilities should consider stocking COVID-19 post-exposure prophylaxis in the onsite/emergency supply of medications, so that course may begin as soon as indicated due to the narrow 72-hour window for starting therapy.

Congregate living facilities should put mechanisms in place to address drug interaction screening and cost-related barriers to timely access to COVID-19 post-exposure prophylaxis. This would include addressing high-cost alert warnings from pharmacy, coupons, patient assistance programs, prior authorizations, and formulary management.

WHAT TO DO IF PATIENT TESTS POSITIVE FOR SARS-COV-2 AFTER STARTING ENSITRELVIR (XOCOVA®)

If a patient initially tests negative for SARS-CoV-2 and is started on ensitrelvir (Xocova®) for post-exposure prophylaxis (PEP) but subsequently tests positive SARS-CoV-2 while completing the PEP course, there are no one-size-fits-all recommendations based on the SCORPIO-PEP data. Clinical management should be determined on a case-by-case basis, taking into consideration the timing of the positive test and/or symptom onset, the patient's risk factors for progression to severe COVID-19, concomitant medications, potential drug interactions, and eligibility for an FDA-approved COVID-19 treatment.

In SCORPIO-PEP, patients who tested positive for SARS-CoV-2 or developed COVID-19 symptoms during the 5-day PEP course were not required to stop or adjust ensitrelvir (Xocova®). However, these findings do not establish ensitrelvir (Xocova®) as a treatment for COVID-19. Ensitrelvir (Xocova®) is FDA-approved for post-exposure prophylaxis and is not approved for treatment of established COVID-19. The observed differences in viral RNA levels and symptom scores were secondary or post-hoc findings and should not be interpreted as evidence of treatment efficacy.

If COVID-19 antiviral treatment is indicated, nirmatrelvir/ritonavir (Paxlovid®) should not be administered concomitantly with ensitrelvir (Xocova®). Concomitant use of nirmatrelvir/ritonavir (Paxlovid®) with ensitrelvir (Xocova®) was prohibited in SCORPIO-PEP because of the potential for a clinically significant drug-drug interaction. Both agents have clinically relevant effects on CYP3A, and the safety and efficacy of concomitant administration have not been established. Selection and timing of COVID-19 treatment should be based on the patient's clinical status, treatment eligibility, and potential drug-drug interactions.

Patients with symptomatic COVID-19 should also be offered management of symptoms with antipyretics, analgesics, antitussives as clinically appropriate for fever, headache, myalgias, and cough.

Repeat PEP courses have not been studied in SCORPIO-PEP. Although pharmacokinetic data show that ensitrelvir (Xocova®) concentrations persist beyond the 5-day course, this pharmacokinetic finding does not establish how long clinical protection lasts or support automatically repeating PEP after Day 10.

WORKFLOW: ENSITRELVIR (XOCOVA®) POST-EXPOSURE PROPHYLAXIS

For LTC and other congregate living settings. Adapt to facility policy, resources, and clinical judgment.
*Please refer to the full protocol for additional guidance and details.

STEP 1*
Confirmed COVID-19 Case Identified
Initiate isolation and infection prevention and control measures per facility policy and current CDC guidance.

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STEP 2*
Conduct the Exposure Assessment
Identify residents and staff with potential exposure to a confirmed COVID-19 case during the infectious period, beginning 48 hours before symptom onset (or positive test if asymptomatic). Did the individual have a qualifying exposure?

→ **NO** → No PEP indicated. Continue routine infection prevention and control measures and symptom monitoring.

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YES → Proceed to Step 3.
Consider duration, ventilation, source control, PPE, and individual risk when assessing exposure.

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STEP 3*
Screen Exposed Individuals and Notify Prescriber
Confirm: age ≥12 years; exposure occurred within 72 hours; symptoms/testing status; risk factors; and current medications for drug-drug interactions/contraindications. Prescribing clinician determines the individual is eligible for ensitrelvir (Xocova®) PEP?

→ **NO** → Do not initiate PEP. Continue infection prevention and symptom monitoring. If symptoms develop or testing is positive, evaluate for COVID-19 treatment per facility protocol.

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YES → Proceed to Step 4.
See Risk Factors and Drug-Drug Interactions resources.

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STEP 4*
Obtain and Fulfill Order
Obtain the order and resolve medication access, cost/prior authorization, and drug-interaction alerts promptly. Give the first dose as soon as possible and within 72 hours of exposure.

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STEP 5*
Administer ensitrelvir (Xocova®)
Day 1: 375 mg (three 125-mg tablets) orally.
Days 2–5: 125 mg (one 125-mg tablet) orally once daily.

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STEP 6*
Monitor and Continue Prevention Measures
Monitor for adverse effects and CYP3A drug interactions. Continue infection prevention and control measures and recommended COVID-19 vaccination.

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New confirmed case identified?
YES → Return to Step 1.
Surveillance continues. Repeat PEP courses for subsequent exposures have not been evaluated.

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DISCLAIMER

This protocol is based on data available at the time of writing (July 2026) and is intended solely as a clinical guidance document for healthcare professionals regarding the use of ensitrelvir (Xocova®) for post-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19. It is not all-encompassing and may not reflect the most recent evidence, regulatory changes, or updates from authoritative bodies. For the most accurate and current information, clinicians should consult CDC, FDA, and other relevant national or international health authority websites and guidelines. This document does not establish a standard of care and is not intended to replace independent clinical judgment, professional expertise, or individualized patient assessment. Patient-specific factors including medical history, comorbidities, allergies, potential drug–drug interactions, renal/hepatic function, the nature and timing of the exposure, and other clinical considerations must always be taken into account when making treatment decisions. Adherence to the recommendations in this protocol is voluntary. ASCP makes no warranties, express or implied, regarding the accuracy, completeness, or applicability of the information contained herein and assumes no responsibility or liability for any injury, loss, or damage arising from its use or application. Users are responsible for verifying all information and exercising their own professional judgment in the care of individual patients.

REFERENCES

1. Xocova (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc. May 2026.
2. Shumaker AH, Bhimraj A, Bedimo R, et al. 2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Antiviral Treatment for Mild to Moderate COVID-19 in Adults. Clin Infect Dis. Published online April 1, 2026. doi:10.1093/cid/ciaf680
3. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir for Covid-19 Postexposure Prophylaxis in Household Contacts. N Engl J Med. 2026;394(19):1905-1915. doi:10.1056/NEJMoa2509306
4. Centers for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic. Updated May 8, 2023.
5. Centers for Disease Control and Prevention. Interim Guidance for Managing Healthcare Personnel with SARS-CoV-2 Infection or Exposure to SARS-CoV-2. Updated March 18, 2024.
6. Shimizu R, Sonoyama T, Fukuhara T, Kuwata A, Matsuo Y, Kubota R. Safety, Tolerability, and Pharmacokinetics of the Novel Antiviral Agent Ensitrelvir Fumaric Acid, a SARS-CoV-2 3CL Protease Inhibitor, in Healthy Adults. Antimicrob Agents Chemother. 2022;66(10):e0063222. doi:10.1128/aac.00632-22
7. CDC. Preliminary Estimates of COVID-19 Burden. Accessed Aug 3, 2026. https://www.cdc.gov/covid/php/surveillance/burden-estimates.html
8. Thompson DC, Barbu MG, Beiu C, et al. The Impact of COVID-19 Pandemic on Long-Term Care Facilities Worldwide: An Overview on International Issues. Biomed Res Int. 2020;2020:8870249. Published 2020 Nov 4. doi:10.1155/2020/8870249
9. Lee D, Counard C, Tang A, Brister S, Ezike N. Notes from the Field: COVID-19-Associated Mortality Risk Among Long-Term Care Facility Residents and Community-Dwelling Adults Aged ≥65 Years - Illinois, December 2020 and January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(24):803-805. Published 2022 Jun 17. doi:10.15585/mmwr.mm7124a4
10. CDC. People with Certain Medical Conditions and COVID-19 Risk Factors. Updated June 11, 2025. Accessed August 10, 2026. https://www.cdc.gov/covid/risk-factors/index.html
11. Ketkar A, Willey V, Glasser L, et al. Assessing the Burden and Cost of COVID-19 Across Variants in Commercially Insured Immunocompromised Populations in the United States: Updated Results and Trends from the Ongoing EPOCH-US Study. Adv Ther. 2024;41(3):1075-1102. doi:10.1007/s12325-023-02754-0
12. Cazé AB, Cerqueira-Silva T, Bomfim AP, et al. Prevalence and risk factors for long COVID after mild disease: A cohort study with a symptomatic control group. J Glob Health. 2023;13:06015. Published 2023 May 12. doi:10.7189/jogh.13.06015
13. Yotsuyanagi H, Ohmagari N, Doi Y, et al. Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19: The SCORPIO-SR Randomized Clinical Trial. JAMA Netw Open. 2024;7(2):e2354991. Published 2024 Feb 5. doi:10.1001/jamanetworkopen.2023.54991
14. "Data on file, Shionogi, Inc." Refer to Shionogi Medical Information at medinfo@shionogi.com

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