HEALTH SERVICES AGENCY

STANISLAUS COUNTY STANDING STRONG

Date: June 3, 2022
To: Medical Care Providers, Healthcare and other Facilities
From: Thea Papasozomenos, MD, MPH, Assistant Health Officer

Please distribute to all providers and relevant staff in your facility

Health Update

Management of Drug Interactions with Paxlovid; COVID-19 Test to Treat sites

COVID-19 antiviral medications for use in outpatients are readily available in Stanislaus County for providers to prescribe to eligible patients. **Stanislaus County Public Health strongly encourages healthcare entities/providers to ensure capacity for provision of appropriate treatment for their patients.**
California has also sponsored Test to Treat sites across the state through the OptumServe testing locations, two of which are currently located in Stanislaus County. These sites allow individuals to get tested for COVID-19, be evaluated by a provider if results are positive, and receive treatment with antiviral pills (Paxlovid or Molnupiravir), if eligible.
At this time, the planned end date for the OptumServe Test to Treat program is June 30, 2022; it is uncertain if the program will be extended past this date.

Guidance for Stanislaus County Providers:

- Paxlovid prescribing aid:
  - Paxlovid, the current preferred COVID-19 therapy for eligible outpatients per the NIH treatment guidelines, has significant drug-drug interaction potential, primarily due to the ritonavir component of its combination formulation of ritonavir-boosted nirmatrelvir. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.
    - The Infectious Diseases Society of America (IDSA) has a resource for clinicians on management of drug interactions with Paxlovid. Please see attached.

- OptumServe Test to Treat; current Stanislaus County sites are:
  - OptumServe – Salida: 4835 Sisk Rd, Salida, CA 95368
  - OptumServe – Turlock: 275 N Orange St., Turlock, CA 95380

Additional Information:

- CDPH COVID-19 Treatments: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/Treatments.aspx
- IDSA Management of Drug Interactions with Nirmatrelvir/Ritonavir (Paxlovid): Resource for Clinicians: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/
- NIH COVID-19 Treatment Guidelines: Therapeutic Management of Nonhospitalized Adults With COVID-19: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Last Updated: May 6, 2022- ***Version 1.1****

Nirmatrelvir/ritonavir has FDA Emergency Use Authorization to treat mild-to-moderate COVID-19 in patients at high risk of progression to severe disease who are ≥12 years of age and weigh ≥40 kg.

In such patients, IDSA guidelines suggest nirmatrelvir/ritonavir be initiated within 5 days of symptom onset. Patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive nirmatrelvir/ritonavir. NIH guidelines also suggest nirmatrelvir/ritonavir for nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk of disease progression.

Given coformulation with ritonavir as a pharmacokinetic booster, there is potential for drug interactions. The following steps can be taken to minimize the risk of drug interactions for those who are eligible and would benefit from nirmatrelvir/ritonavir treatment:

1. Obtain a complete list of the patient's current medications, including over-the-counter agents and herbal supplements.
2. Confirm that the patient is taking each medication as prescribed. If the patient is not taking a medication, discontinue the medication from their medication profile.
3. Review the FDA Paxlovid® Healthcare Provider Fact Sheet to Identify any medications that the patient is currently taking that are contraindicated with nirmatrelvir/ritonavir. If the patient is taking a contraindicated medication, prescribe alternative treatment for mild to moderate COVID-19.
4. Review potential drug interactions between nirmatrelvir/ritonavir and the patient's current medications.

   Resources:

   - Liverpool COVID-19 Interactions (covid19-druginteractions.org)
   - Paxlovid® Healthcare Provider Fact Sheet
   - PAXLOVID® Patient Eligibility Screening Checklist Tool for Prescribers (fda.gov)
   - Nirmatrelvir/Ritonavir (Paxlovid®): What Prescribers and Pharmacists Need to Know - Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)
5. Advise the patient on dose adjustments, temporary cessation of medication(s), or clinical monitoring that is needed during and after the 5 day nirmatrelvir/ritonavir treatment.
6. If relapse occurs after initial treatment and a second course of treatment is warranted, duration of therapy should be used to guide adjustments to concomitant medications.

**Version 1.1 contains the following correction: "200" has been changed to "100" in the sentence that originally read, "Among the top 200 prescribed drugs, only two have interactions so severe that nirmatrelvir/ritonavir should be avoided altogether: rivaroxaban and salmeterol."*

Among the top 100 prescribed drugs, **only two have interactions so severe that nirmatrelvir/ritonavir should be avoided altogether: rivaroxaban and salmeterol**.

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Rivaroxaban	↑	Increased bleeding	Avoid nirmatrelvir/ritonavir
Salmeterol	↑	Increased cardiac effects	Avoid nirmatrelvir/ritonavir

The following table contains information on management of commonly prescribed medications that are known to interact with nirmatrelvir/ritonavir. This list was derived from ClinCalc's Top 200 Prescribed Medications in the United States in 2019. Please note:

- Inclusion on this list is not a contraindication to prescribe nirmatrelvir/ritonavir. Rather, additional management considerations may be necessary as shown below.
- If a drug is not on this list, it should still be checked for interactions, as it may be a less commonly prescribed medication that has interactions or is contraindicated.
- Routine lab testing for transaminases or creatinine is not needed, and clinical judgement should be used.

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Alprazolam	↑	Excess sedation	Consider dose reduction, but do not stop if chronic use
Apixaban	↑	Increased bleeding	Dose dependent: • Apixaban 2.5 mg: Avoid nirmatrelvir/ritonavir • Apixaban 5mg or 10 mg: Reduce dose by 50% until 3 days after nirmatrelvir/ritonavir
Bupropion	↓	Decreased effects	No dose adjustment required
Buspirone	↑	Increased side effects	Reduce dose or monitor for side effects
Calcium-channel blockers (amlodipine, nifedipine)	↑	Decreased blood pressure	• Continue if tolerated based on symptoms • Reduce dose if patient has low blood pressure
Calcium-channel blockers (diltiazem, verapamil)	↑	Decreased blood pressure	• Continue if tolerated • Reduce dose if patient has low blood pressure or bradycardia
Clonazepam	↑	Excess sedation	Consider dose-reduction, but do not stop if chronic use

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Clopidogrel	↓	Increased clotting	• Avoid nirmatrelvir/ritonavir for 6 weeks after coronary stenting • Other patients: No change
Diazepam	↑	Excess sedation	Consider dose reduction, but do not stop if chronic use
Hormonal contraceptives with ethinyl estradiol	↓	Lack of contraceptive efficacy	Recommend nonhormonal contraception until one menstrual cycle after nirmatrelvir/ritonavir
Hydrocodone Oxycodone (with or without acetaminophen)	↑	Increased opioid side effects, sedation	Consider reducing frequency of dosing or reduced dose of hydrocodone/oxycodone
Isosorbide mononitrate	↓	Decreased active drug	No dose adjustment required
Paroxetine	↓	Decreased effects	No dose adjustment required
Quetiapine	↑	Increased effects	Reduce dose of quetiapine to one-sixth of the original dose during nirmatrelvir/ritonavir treatment
Risperidone	↑	Increased toxicity	No dose adjustment; monitor for adverse effects
Rivaroxaban	↑	Increased bleeding	Avoid nirmatrelvir/ritonavir
Salmeterol	↑	Increased cardiac effects	Avoid nirmatrelvir/ritonavir
Statins (HMG-CoA reductase inhibitors)	↑ **most statins**	Increased toxicity	Hold statins during nirmatrelvir/ritonavir course and for 5 days after
Steroids, inhaled or nasal	↑	Increased toxicity	No dose adjustment required
Steroids, oral	↑	Increased toxicity	No specific adjustment; consider reducing the dose
Tamsulosin	↑	Hypotension, orthostasis	Dose-dependent: • Tamsulosin 0.4 mg: No change (monitor blood pressure) • Tamsulosin 0.8 mg: Consider holding or decrease to 0.4 mg
Tramadol	↓	Decreased effects, increased side effects	No dose adjustment required

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Trazodone	↑	Sedation, hypotension	No dose adjustment required; consider reducing dose if risk for falls
Warfarin	**Variable**	Unpredictable effects on INR	Monitor INR for dose adjustment
Valsartan	↑	Hypotension	No dose adjustment required; consider reducing dose if risk of hypotension

Nirmatrelvir/Ritonavir Renal Dosing Guide:

Estimated Glomerular Filtration Rate (eGFR)*	Nirmatrelvir Dose	Ritonavir Dose
> 60 mL/min	300 mg every 12 hours x 5 days	100 mg every 12 hours x 5 days
≥ **30 to < 60 mL/min**	150 mg every 12 hours x 5 days	100 mg every 12 hours x 5 days
< 30 mL/min	Nirmatrelvir/ritonavir not recommended	
* eGFR calculated by CKD-EPI Creatinine Equation (eGFR Calculator | National Kidney Foundation)		

References

Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid®. Accessed May 2, 2022. https://www.fda.gov/media/155050/download

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