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COVID-19 OUTPATIENT THERAPEUTICS TOOLKIT

A GUIDE FOR CLINICIANS

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MICHIGAN.GOV/COVIDTHERAPY

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Executive Summary

The Michigan Department of Health and Human Services (MDHHS) has developed this toolkit to provide condensed, easy to use information on outpatient medications for the treatment and pre-exposure prophylaxis of COVID-19 in certain high-risk patients. This toolkit does not include all information found in the Emergency Use Authorizations (EUA), and all providers should consult the applicable EUA Fact Sheet for important prescribing drug information such as drug interactions, adverse reactions and specific EUA criteria not included in each individual medication section below.

The purpose of this toolkit is to provide a clinically focused overview of outpatient medications used to treat mild to moderate COVID-19 in patients at risk for hospitalization or death and for pre-exposure prophylaxis (prevention) in certain people with moderate to severe immunocompromising conditions and for the few who have experienced a severe reaction to the COVID-19 vaccine. It is designed to provide clinicians with quick reference guides for each of the medications currently authorized for outpatient use. The medications in this tool kit include monoclonal antibodies (mAb) and antiviral therapies. The preferred order of treatment (#1-6 below) based on eligibility and availability is as follows:

1. Paxlovid (given orally over five days and needs to be started within five days of symptom onset).
2. Remdesivir (given by IV infusion for three consecutive days when started within seven days of symptom onset).
3. Bebtelovimab (given by single IV injection when started within seven days of symptom onset).
4. Molnupiravir (given orally for five days and needs to be started within five days of symptom onset).
5. Evusheld (given by two intramuscular injections for pre-exposure prophylaxis in patients including those with moderate/severe immunocompromise or an inability to receive COVID vaccination).

Regarding medications used for treatment, it is important to remember that the FDA has indicated in their EUAs that these medications are intended for those who are at increased risk of hospitalization or death ***and are not hospitalized when treatment is started***.

Those who are immunocompromised or not up to date[1] on the COVID-19 vaccine are particularly at risk and those with any of the following conditions identified in the EUAs, as well as the expanded CDC criteria linked below:

[1] Stay Up to Date with Your Vaccines

- Older age (for example ≥65 years of age)
- Obesity (e.g., BMI >25 kg/m2), or BMI ≥85th percentile pediatrics
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (e.g., COPD, moderate to severe asthma, etc.)
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy) or other complexity conditions
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy)
- Other conditions identified by the CDC for the person at risk for disease severity

Additional Resources

U.S. Department of Health and Human Services COVID-19 Monoclonal Antibody Therapeutics Digital Toolkit:
https://www.phe.gov/emergency/events/COVID19/therapeutics/toolkit/Pages/default.aspx

American College of Emergency Physicians Monoclonal Antibody Toolkit:
https://www.acep.org/corona/COVID-19-alert/covid-19-articles/monoclonal-antibody-toolkit/

Medication Cards

The medication cards below are intended to serve as a quick reference tool for clinicians. They do not take the place of important additional information provided in the applicable FDA Fact Sheet for Healthcare Providers. Below are the links to the EUAs for the medications included in the toolkit:

- Paxlovid
- Remdesivir
- Bebtelovimab
- Molnupiravir
- Evusheld

Paxlovid

Prescribers must comply with requirements of the FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid. Patients must have tested positive for SARS-CoV-2. PAXLOVID is indicated 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), and

- with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and
- who are at high risk for progression to severe COVID-19, including hospitalization or death.

Dosing of PAXLOVID (see full Fact Sheet for Healthcare Providers)

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co-administered with ritonavir.

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.
- Administer orally with or without food.
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days.
- Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days.
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min).
- PAXLOVID is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).
- Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2.

Dosage Forms of PAXLOVID

- Tablets: nirmatrelvir 150 mg
- Tablets: ritonavir 100 mg

Warning and Precautions for PAXLOVID

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions.
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir.
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.
- There is insufficient human data on Paxlovid in pregnancy. See the Fact Sheet for additional information. Paxlovid should be used with caution in pregnancy and only when mAb therapy is unavailable and after full discussion with patient of potential risks and benefits.

Contraindications for PAXLOVID

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components.
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.
- Co-administration with 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.

COVID-19 OUTPATIENT THERAPY

Guidance for outpatient management of patients with mild to moderate COVID-19.

Molnupiravir

Prescribers must comply with requirements of the FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Molnupiravir. Patients must have tested positive for SARS-CoV-2. Molnupiravir is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (18 years of age), and

- with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and
- who are at high risk for progression to severe COVID-19, including hospitalization or death, and
- for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Dosing and Administration of Molnupiravir (see full Fact Sheet for Healthcare Providers)

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.
- Take molnupiravir as soon as possible after a diagnosis of COVID19 has been made, and within 5 days of symptom onset.
- Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.
- Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

Dosage Forms of Molnupiravir

- Capsules: 200 mg

Warning and Precautions for Molnupiravir

- Use in Pregnancy /Embryo-Fetal Toxicity: Molnupiravir is not recommended for use during pregnancy.
- Bone and Cartilage Toxicity: Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

Contraindications for Molnupiravir

- No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.
- Not to be used in pregnancy

Medication Interactions with Molnupiravir

- No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.

Monoclonal Antibodies

Monoclonal antibodies (mAb) are for use in non-hospitalized patients aged 12 years and older who are at high risk for severe COVID-19 related illness and weigh at least 40kg and are experiencing mild to moderate COVID-19 symptoms. Monoclonal antibodies should be given within 7 days of symptom onset.

Indications for the Administration of Monoclonal Antibodies:

- All patients must have a positive COVID-19 PCR or Antigen test (including home test).
- Outpatient- not hospitalized for COVID-19.
- No requirement for supplemental oxygen.

mAb Therapeutics IV Administration

- Obtain baseline vital signs prior to infusion
- Monitor patient for 1 hour post administration.
- Obtain post administration vitals.
- Monitor for worsening/adverse reactions such as worsening COVID-19 symptoms, low-grade fever, myalgias, headache, and itching.
- Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs. Rash, diarrhea, nausea, dizziness, and pruritis have also been reported.

Bebtelovimab is authorized for use 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, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Bebtelovimab

For IV infusion of Bebtelovimab:

- 175 mg of Bebtelovimab administered as a single intravenous injection over at least 30 seconds.
- After the entire contents of the syringe have been administered, flush with 0.9% Sodium Chloride to ensure delivery of the required dose.

Special Considerations

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities. Medical conditions or other factors (e.g., race or ethnicity) that are not listed in the mAb EUAs may also be associated with high risk for progression to severe COVID-19 Anti-SARS-CoV-2 Monoclonal Antibodies | COVID-19 Treatment Guidelines

The current EUAs state that the use of anti-SARS-CoV-2 mAbs may be considered for patients with high-risk conditions and factors that are not listed in the EUAs. For additional information on medical conditions and other factors that are associated with increased risk for progression to

severe COVID-19, see the CDC webpage People With Certain Medical Conditions. The decision to use anti-SARS-CoV-2 mAbs for a patient should be based on an individualized assessment of risks and benefits.

Considerations in Pregnancy

The use of anti-SARS-CoV-2 mAbs can be considered for pregnant people with COVID-19, especially those who have additional risk factors for severe disease. Pregnancy information for each individual mAb can be found in the EUA.

As immunoglobulin (Ig) G mAbs, the authorized anti-SARS-CoV-2 mAbs would be expected to cross the placenta. There are no pregnancy-specific data on the use of these mAbs; however, other IgG products have been safely used in pregnant people when their use is indicated.

Therefore, authorized anti-SARS-CoV-2 mAbs should not be withheld during pregnancy. When possible, pregnant and lactating people should be included in clinical trials that are evaluating the use of anti-SARS-CoV-2 mAbs for the treatment and/or prevention of COVID-19.

Considerations in Children

Clinicians and health systems choosing to use these agents on an individualized basis should consider risk factors supported by pediatric-specific evidence and ensure the implementation of a system for safe and timely administration that does not exacerbate existing health care disparities.

Children | COVID-19 Treatment Guidelines

Remdesivir

Remdesivir Prescribing

Remdesivir is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for the treatment COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

- Hospitalized.
- Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Dosage and Administration

For adults and pediatric patients ≥12 years old and weighing ≥40 kg: 200 mg who are non-hospitalized and diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death the recommended total treatment duration is 3 days.

- The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.
- Administer remdesivir via intravenous (IV) infusion over 30 to 120 minutes.
- Remdesivir is not recommended in patients with eGFR less than 30 mL per minute.

When considering the transition to outpatient remdesivir, some logistical constraints should be addressed:

- Because remdesivir requires IV infusion for 3 consecutive days, it may make it difficult to administer the drug in some settings.
- Remdesivir should be administered in a setting where the treatment of severe hypersensitivity reactions, such as anaphylaxis, is possible. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion.
- Remdesivir is currently FDA-approved for hospitalized individuals; however, use of the drug for outpatient treatment would be an off-label indication.

Warnings and Precautions

Hypersensitivity, including infusion-related and anaphylactic reactions:

- Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of remdesivir. Monitor patients under close medical supervision for hypersensitivity reactions during and following administration of remdesivir.
- Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever,dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering.
- Slower infusion rates (maximum infusion time ≤120 minutes) can potentially prevent these reactions. If a severe infusion-related hypersensitivity reaction occurs, immediately discontinue remdesivir and initiate appropriate treatment.
- Increased risk of transaminase elevations: Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received remdesivir these elevations have also been reported as a clinical feature of COVID-19. Perform hepatic laboratory testing in all patients (see dosage and administration). Consider discontinuing Remdesivir if ALT levels increase to >10x ULN. Discontinue Remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- Risk of reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine: Coadministration of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments, demonstrating potential antagonism, which may lead to a decrease in the antiviral activity of remdesivir.

Pregnancy and Lactation

Pregnancy: There are insufficient human data on the use of remdesivir during pregnancy. Pregnant women hospitalized with COVID-19 are at risk for serious morbidity and mortality. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Lactation: It is not known whether remdesivir can pass into breast milk. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Dosage Preparation and Administration									
Dose Reconstitution				**Dose Reconstitution**					
Remdesivir for injection, 100 mg/vial,lyophilized powder must be reconstituted with 19 mL Sterile Water for Injection and diluted in a 100 mL or 250 mL 0.9% sodium chloride infusion bag prior to administration. Red cap on vial				**Remdesivir injection, 100 mg/20 mL (5mg/mL)** solution must be diluted in a 250 mL 0.9%sodium chloride infusion bag prior to administration. Blue cap on vial *****Only use the solution formulation for patients weighing at least 40 kg*****					
Dilution				**Dilution**					
Remdesivir dose	0.9% sodium chloride infusion bag volume to be used	Volume tobe withdrawnand discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted Remdesivir for injection	Remdesivir	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of Remdesivir injection		
Loading dose 200 mg (2 vials)	250 ml 100 ml	40 ml	40 ml (2 x 20ml)	Loading dose 200mg (2 vials)	250 ml	40ml	40 ml (2 x 20 ml)		
Maintenance dose100 mg (1 vial)	250 ml 100 ml	20 ml	20 ml	Maintenance dose 100 mg (1 vial)		20 ml	20 ml		
Infusion Bag Volume	Infusion Time	Rate of Infusion		Infusion Bag Volume	Infusion Time	Rate of Infusion			
250 ml	30 minutes	8.33 ml/min		250 ml	30 minutes	8.33 ml/min			
	60 minutes	4.17 ml/min			60 minutes	4.17 ml/min			
	120 minutes	2.08 ml/min			120 minutes	2.08 ml/min			
100 ml	30 minutes	3.33 ml/min							
	60 minutes	1.67 ml/min							
	120 minutes	0.83 ml/min							

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Guidance for outpatient management of patients with mild to moderate COVID-19.

Evusheld

Evusheld (tixagevimab/cilgavimab) is a long-acting monoclonal antibody available under EUA by the FDA for COVID-19 pre-exposure prophylaxis (PrEP) in certain high-risk, immunocompromised individuals and those unable to receive the COVID-19 vaccine because of a previous severe reaction.

Evusheld Prescribing

1) Per the FDA EUA, Evusheld may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under Michigan law to prescribe drugs in the therapeutic class to which Evusheld belong (monoclonal antibodies). See full applicable Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on alternatives.
2) The dosage of EVUSHELD for emergency use is:
    - Initial dose: 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections.
3) ***Repeat dose:*** The SARS-CoV-2 variants that will be circulating in the U.S. when Evusheld may need to be redosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available.
4) Evusheld may be given to individuals >12 years old and weighing at least 40kg who are not currently infected with COVID-19, have not had a known exposure to someone with SARS-CoV-2 and:
    - May NOT mount an adequate immune response to COVID-19 vaccination.
    - May not be eligible for COVID-19 vaccination due to a history of severe adverse reaction (severe allergic reaction) to either the COVID-19 vaccine, or the COVID-19 vaccine components.
    - Have moderate to severe immune compromise related to a medical condition or receipt of immunosuppressive medications or treatments.
    - Evusheld PrEP is not a substitute for vaccination.

Operationalizing the Administration of Evusheld

Because health care organizations are unique, operationalizing access to Evusheld may be done in different ways within the health care system. This is a formative process that will need to be adapted and revised over time to best serve high-risk patients. Health care systems should consider the following, in consultation with their scarce resource allocation committees, when establishing policies for Evusheld administration to qualifying patients.

Identify and Screen Potentially Eligible Patients

- Health care providers and health systems should work to identify their patient population eligible to receive Evusheld.
- Patient screening should be done to determine eligibility for Evusheld. This can be accomplished through an electronic medical record search for appropriate conditions (ICD-10 codes)
- Pharmacy identification of patients currently receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab).
- Outreach to clinics and specialty physician offices asking them to identify patients who meet the eligibility criteria (rheumatology, oncology, hematology, transplant services).
- Using a list of identified and screened patients, those meeting the criteria should be placed in the order to receive Evusheld.
- After identifying patients who have opted to receive Evusheld, a qualified health care provider or designee should contact each patient and:
    - Provide counseling on the potential risks and benefits of Evusheld and provide a copy of the Fact Sheet for Patients and Caregivers.
    - Provide instructions for scheduling and administration.

Administering and Monitoring Evusheld

- Once patients have been selected and agree to receive Evusheld, an order will be provided by an authorized healthcare provider. The medication should be provided to the site of administration and an appointment should be scheduled.
- Evusheld is administered as directed by the FDA fact sheet for healthcare providers.
- Patients must be observed for at least 60 minutes following administration.
- The current EUA calls for the re-administration of Evusheld every six months to sustain pre- exposure prophylaxis. However, it is unknown what SARS-CoV-2 variants that will be circulating in the United States when Evusheld may need to be redosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available.
- Health care systems should monitor patients receiving Evusheld for safety and effectiveness in preventing COVID-19 infections, especially hospitalizations or deaths.

Evusheld Warnings and Precautions

Hypersensitivity Including Anaphylaxis

- Serious hypersensitivity reactions, including anaphylaxis, have been observed with Human immunoglobulin G1 (IgG1) monoclonal antibodies like Evusheld. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur while taking Evusheld, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after injections and observe for at least one hour.

Clinically Significant Bleeding Disorders

- As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

Cardiovascular Events

- In PROVENT (LB5. PROVENT: Phase 3 Study of Efficacy and Safety of AZD7442 (Tixagevimab/Cilgavimab) for Pre-exposure Prophylaxis of COVID-19 in Adults (nih.gov) there was a higher rate of cardiovascular serious adverse events (SAEs), including myocardial infarction (one fatal SAE) and cardiac failure, in subjects who received Evusheld compared to placebo. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern.
- A causal relationship between EVUSHELD and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies. Consider the risks and benefits prior to initiating Evusheld in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

Drug Interaction

Drug-drug interaction studies have not been performed. Tixagevimab and cilgavimab are not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Use in Specific Populations

Pregnancy

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Nonclinical reproductive toxicity studies have not been conducted with tixagevimab and cilgavimab. In a tissue cross-reactivity study assessing off-target binding of tixagevimab and cilgavimab to human fetal tissues no binding of clinical concern was observed. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, tixagevimab and cilgavimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of tixagevimab and cilgavimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation

There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evusheld and any potential adverse effects on the breastfed infant from EVUSHELD.

Pediatric Use

EVUSHELD is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of EVUSHELD have not been established in pediatric individuals. The dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the trials PROVENT and STORM CHASER Phase III Double-blind, Placebo-controlled Study of AZD7442 for Post- Exposure Prophylaxis of COVID-19 in Adults - Full Text View - ClinicalTrials.gov

Geriatric Use

Of the 2,029 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 23% (N= 461) were 65 years of age or older and 3.3% (N= 67) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger subjects.

Renal Impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

Hepatic Impairment

The effect of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

Other Specific Populations

Based on a population PK analysis, the PK profile of tixagevimab and cilgavimab was not affected by sex, age, race, or ethnicity. Population PK model-based simulations suggest that body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in healthy adults over the range of 36 kg to 177 kg.

Medication Crosswalk

	Paxlovid	Remdesivir	Bebtelovimab	Molnupiravir
Basic Mechanism	Antiviral –protease inhibitor	Antiviral – RNA polymerase inhibitor	Neutralizing monoclonal antibody	Antiviral – Mutagenic
Core FDA Requirements per EUA				
FDA Fact Sheets for:	Paxlovid	Remdesivir	Bebtelovimab	Molnupiravir
Route of administration	Oral	IV infusion x3d	IV injection	Oral
Use in mild to moderate COVid-19	Yes	Yes	Yes	Yes
Use for pre/post exposure prophylaxis	No	No	No	No
Days to start from symptom onset[1]	5 days	7 days	7 days	5 days
Days of therapy / number of treatments	5 days	3 days	1 treatment	5 days
Must test positive for SARS-CoV-2[2]	Yes	Yes	Yes	Yes
Minimum age / weight	≥12 YO/40 kg	/≥3.5 kg	≥12 YO/40 kg	≥18 YO/
Use if Hospitalized FOR COVID-19	No[3]	Yes[3]	No	No[3]
Use if receiving oxygen FOR COVID-19	N/A	Yes	No	N/A
Use if receiving increase in chronic non-COVID oxygen therapy due to COVID-19	N/A	Yes	No	N/A
Patient must be at high risk for progression to severe COVID-19, including hospitalization or death	Yes (per CDC)	Yes (per CDC)	Yes (per CDC)	Yes (per CDC)
Use only when other therapy unavailable	N/A	N/A	N/A	Yes
Clinical Considerations Per FDA EUA				
Drug interactions	See Guide	See Fact Sheet	Unlikely	None known
Contraindications[4]	See Fact Sheet	None known	None known	None known
Renal impairment – moderate (eGFR ≥30 to ≤60 mL/min)	Dose reduction	See Fact Sheet	No dosing change	No dosing change
Renal impairment – severe (eGFR<30 ml/min)	Not recommended	See Fact Sheet	No dosing change	No dosing change
Hepatic impairment (severe=Child-Pugh Class C)	Not recommended in severe	Unknown -hepatic testing before starting	Unknown in moderate to severe	No dosing change
Pregnancy	Risk vs. benefit See Fact Sheet	Risk vs. benefit See Fact Sheet		Not recommended

	Paxlovid	Remdesivir	Bebtelovimab	Molnupiravir
Dosing Per FDA EUA				
Dosing – Standard • Non-hospitalized patients • Age ≥12 YO and weight ≥40 kg • Follow FDA Fact Sheet instructions for all medications o Laboratory testing required before treatment with remdesivir	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days.	Day 1: 200 mg IV infusion Day 2 and 3: 100 mg IV infusion Infuse over 30-120 minutes. Obtain hepatic function tests and prothrombin time before giving.	Bebtelovimab 175 mg administered as a single intravenous injection over at least 30 seconds.	**Only for age ≥18 YO** 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.
Dosing – Pediatric • Non-hospitalized patients • Age <12 YO and weight <40 kg and ≥3.5 kg) • Follow FDA Fact Sheet instructions for all medications o Laboratory testing required before treatment with remdesivir	N/A	Day 1: 5 mg/kg IV infusion. Day 2 and 3: 2.5 mg/kg IV infusion. In pediatric patients use Lyophilized Powder for Injection only.	N/A	N/A
Dosing – Moderate renal impairment (eGFR ≥30 to <60 mL/min) • Follow FDA Fact Sheet instructions o Laboratory testing required before treatment with remdesivir	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days.	See Fact Sheet	N/A	N/A
1. The first day of symptoms is considered Day 0. 2. Positive test for SARS-CoV-2 includes both antigen and PCR. Patient/parent attestation to positive home test is acceptable. 3. Patients requiring hospitalization for COVID-19 after starting treatment may complete the full 5-day treatment course per the health care provider's discretion. 4. Hypersensitivity reaction to medication in past is a contraindication.				

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