PRIORITY ELIGIBILITY CRITERIA FOR COVID-19 OUTPATIENT THERAPY

Guidance for high-risk non-hospitalized patients with mild to moderate COVID-19

Michigan.gov/Coronavirus

Updated 1-28-22

Background

Over the course of the last year, the FDA has issued Emergency Use Authorizations (EUA) for multiple therapeutics for the treatment or prevention of COVID-19 in children and adults. Initially, the FDA authorized bamlanivimab, a single monoclonal antibody (mAb) therapy and then expanded to three mAb-therapies, bamlanivimab/etesevimab, REGEN-COV and sotrovimab, for the treatment of COVID-19 in children and adults with mild-to-moderate symptoms and who are at high risk for progression to severe illness including hospitalization and death. With the emergence of Omicron variants, efficacy of two of the three mAb therapies diminished, with sotrovimab the only currently authorized mAb therapy.

In December 2021, two new oral antiviral therapies, Paxlovid and molnupiravir were authorized for use under EUAs for treatment of mild to moderate COVID-19. Recently, remdesivir, an intravenous antiviral used successfully for treatment of hospitalized COVID-19 patients, was recommended by the NIH treatment panel for outpatient treatment of patients with mild to moderate COVID-19. Finally, Evusheld, a long-acting mAb was authorized for the prevention of COVID-19 (pre-exposure prophylaxis) in patients who are moderate to severely immunocompromised or have had a severe reaction to COVID vaccine. While not a substitution for vaccination, these medications represent important new approaches to reducing hospitalizations and preventing deaths in high-risk patients who qualify.

Overarching Goal

The primary goal of the outpatient therapy is to reduce hospitalizations or deaths in high-risk COVID-19 patients and to reduce the impact on Michigan's healthcare system.

Priority Eligibility Criteria for COVID-19 Outpatient Therapy

MDHHS has established *Priority Eligibility Criteria for COVID-19 Outpatient Therapy* (see Appendix A) to assure those who are at higher risk of hospitalization or death receive priority access to these medications. These criteria have been modified from the 4-tier NIH recommended prioritization criteria[1]. The modifications include establishing sub-tiers for Tier 1 and 3, expanding eligibility from those who are unvaccinated (NIH) to those who are not up to date with vaccinations for their age (including boosters). Pregnancy is included in those who are not up to date on vaccinations in Tier 1B. Using the Michigan High-Risk Criteria are felt to be more predictive of those at risk for hospitalization or death than the FDA's CDC-based criteria which are considered to be overly broad. MDHHS has also established a separate 2-tiered set of priority eligibility criteria for Evusheld that is consistent with NIH criteria for this medication (see Appendix E). As supply and/or demand change, the eligibility criteria for these medications will be revised accordingly.

[1] Statement on Therapies for High-Risk, Nonhospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)

Preferential Order of Medication Use

Per the NIH Treatment Panel's recommendation[2], medications used for treating mild to moderate COVID-19 in high-risk patients should be used in the following preferential order, based on eligibility and availability of medications:

- Oral Paxlovid (must be started within 5 days of symptom onset)
- IV sotrovimab (must be administered within 10 days of symptom onset)
- IV Remdesivir (must be started within 7 days of symptom onset)
- Oral Molnupiravir (must be started within 5 days of symptom onset).

Ethical Use of Medications

Given the limited availability of these medications, it is essential that all prescribers apply ethical principles in determining eligibility for these medications. Medications should only be prescribed in bonified clinician-patient relationships. Additional information on ethical principles during scarce resource allocations can be obtained through MDHHS[3].

Additional Information

Additional information on these medications can be obtained through the MDHHS website at www.michigan.gov/covidtherapy selecting "For Healthcare Providers". Questions may be submitted by email to mdhhs-covid-therapies@michigan.gov.

Oral Antiviral Medication

This document provides information on priority eligibility and prescribing requirements for the use of the oral antiviral medications PAXLOVID[4] and molnupiravir[5], both currently under EUA by the FDA for the outpatient treatment of mild to moderate COVID-19. Prescribers must adhere to the requirements specified in the applicable FDA Fact Sheet for Healthcare Providers and with the MDHHS Priority Eligibility Criteria (Appendix A). Prescribers are responsible for ordering these medications for their patients in accordance with these documents.

Authorized Prescribers: Per the FDA EUA, both medications 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 PAXLOVID and molnupiravir belong (i.e., anti-infectives).

See full applicable Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on alternatives, and additional information on COVID-19.

Medications Not Approved: Both medications are authorized but not approved for any use, including for use as treatment of COVID-19. They may only be administered under the EUA specifications, and not "off label". They are not approved for preventative or prophylactic purposes.

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[2] Statement on Therapies for High-Risk, Nonhospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)
[3] Michigan Guidelines for Implementation of Crisis Standards of Care and Ethical Allocation of Scarce Resources (MDHHS)
[4] EUA 105 Pfizer Paxlovid LOA (12222021) (fda.gov)
[5] Molnupiravir LOA 12232021 (fda.gov)

Limitations of Authorization Use:

- PAXLOVID and molnupiravir are not authorized in patients under 12 and 18 years of age, respectively.
- Medications are not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- Medications are not authorized for pre-exposure or post-exposure prophylaxis of COVID-19.
- Medications are not authorized for use longer than 5 consecutive days.

Prescribing Requirements

Because of the limited availability of these medications, certain requirements for prescribing are needed to assure that those at highest risk have access to these medications including:

1. Prior to prescribing, must communicate to the patient and/or caregiver information consistent with the applicable "FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS" and provide them with a copy (electronically is acceptable) of this prior to prescribing the medication.
2. Prescriber needs to determine closest dispensing pharmacy that has product.
    - For a list of pharmacies dispensing antiviral medication and current availability go to: https://rx.meijer.com/covid19/therapeuticprogram
3. Electronic prescriptions are preferred.
4. Telephone prescriptions will not be accepted.
5. Paper prescriptions (including faxed) using the MDHHS prescription template or other prescription form may be used but must have required information including patient's phone number and qualifying criteria as described below.
6. In addition to standard prescribing information, prescriptions must specify in the comments/ notes section:
    a) The specific applicable Priority Eligibility Criteria validating the high-risk condition that qualifies for medication administration.
        1) e.g., "Eligibility: Immunocompromised secondary to taking rituximab"
        2) e.g., "Eligibility: not up to date on COVID vaccines and age 67"
        3) e.g., "Eligibility: Up to date on COVID vaccines, and age 79"
    b) The date of symptom onset (antiviral medication must be started within 5 days of symptom onset). Note: The initial day of symptom onset is considered "Day 0".
    c) Prescriptions lacking this information will not be filled and may delay or prevent access to therapy.

Antiviral Therapy Dispensing Sites

- Paxlovid* currently has limited availability through the following sites:
    - Selected Federally Qualified Health Centers and Tribal Health Centers
    - Selected Meijer Pharmacies throughout Michigan
    - Selected retail pharmacies in areas not served by Meijer
- Molnupiravir** currently has limited availability through the following sites:
    - All Meijer Pharmacies
    - Selected retail pharmacies in areas not served by Meijer

*Specific drug information for Paxlovid can be found in Appendix B.
**Specific drug information for molnupiravir can be found in Appendix C.

Monoclonal Antibody Therapy

Treatment with mAb continues to be an important therapy for mild to moderate COVID infection and is preferred over treatment with molnupiravir whenever it can be readily accessed. Based on current evidence, mAb therapy is also a comparable alternative to Paxlovid for patients who do not have access to the oral medication, have contraindications to the medication, or are beyond 5 days (but within 10 days) of symptom onset. Treatment with mAb should be considered for patients who are in eligible lower risk tiers in the Priority Eligibility Criteria. Clinicians should maintain awareness of locations administering mAb therapy to support timely referrals for their patients. Additional information on mAb sites can be found on www.michigan.gov/covidtherapy.

Throughout the last year, monoclonal antibody (mAb) therapy has become essential for treating individuals who are experiencing mild-to-moderately severe COVID-19 and meet high risk criteria outlined in the FDA EUA. Bamlanivimab/etesevimab and REGEN-COV have been highly effective against past variants. However, these medications do not have activity against the Omicron variant and have recently had their EUAs revised by the FDA. These medications should not be used until such time as the FDA once again revises the EUA to authorize their use in response to new variants in which they are likely to demonstrate effectiveness. Healthcare facilities with a supply of these medications are asked to retain the product in the event the medications are reauthorized. Sotrovimab is currently the only authorized mAb medication for treatment of COVID-19.

Considerations in the Use of Sotrovimab

1. While sotrovimab remains available in limited quantities, similar to new antiviral medication, clinicians prescribing COVID-19 therapy must follow the current MDHHS Priority Eligibility Criteria for COVID-19 Outpatient Therapy (Appendix A). Revisions in these criteria will be made and communicated, as appropriate.
    a) Healthcare systems may enact more restrictive criteria if determined to be necessary by their Scarce Resource Allocation (or similar) Committee.
    b) Future statewide or regional changes in prioritization levels will occur based on available supply, current demand, dominant variant, and other clinical/epidemiologic considerations.
2. Sotrovimab must be administered intravenously within 10 days of symptom onset.
3. Sites receiving sotrovimab must agree to meet MDHHS performance expectations including:
    a) Treat patients regardless of insurance status or ability to pay
    b) Treat patients regardless of health system affiliation
    c) Compliance with MDHHS Priority Eligibility Criteria (Appendix A)
    d) Compliance with federal and state reporting requirements, including completion of the MDHHS Patient Profile Form
4. Failure to comply with federal and state reporting requirements, may lead to decreased or withheld future allocations.

IV Remdesivir for Non-Hospitalized Patients

Since receiving an EUA in May 2020 and subsequently receiving full FDA approval, remdesivir has been used as a safe and effective treatment for COVID-19 in certain hospitalized patients. Recently, the NIH added a 3-day course of IV remdesivir as an alternative treatment option for non-hospitalized, high-risk patients with mild to moderate COVID-19. Subsequently, the FDA has expanded the approved clinical indication for remdesivir to **include its use in adults and pediatric patients (12 years of age and older who weigh at least 40 kilograms, which is about 88 pounds) with positive results of direct SARS-CoV-2 viral testing, and who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death[6].**

As Omicron has become the dominant variant in Michigan, and given the shortage of Paxlovid and sotrovimab, the expansion of Remdesivir to the outpatient setting is warranted. Remdesivir is expected to retain activity against the Omicron variant. Therefore, providers should consider a three-day course of remdesivir, as appropriate. The PINETREE[7] study was a randomized, placebo-controlled trial in non-hospitalized patients with COVID-19 who were at high risk of clinical progression and were within 7 days of symptom onset and received 3 days of IV remdesivir or placebo. The study found a 4.6% absolute reduction and an 87% relative reduction in the risk of hospitalization or death in those receiving remdesivir (HR 0.13; 95% CI, 0.03–0.59; P = 0.008), comparable to both Paxlovid and sotrovimab.

Considerations in Using Remdesivir in Non-Hospitalized Patients:

- Because remdesivir requires IV infusion for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings.
- Remdesivir is approved by the FDA for use in non-hospitalized individuals.
- Remdesivir should be administered in a setting where severe hypersensitivity reactions (e.g., anaphylaxis), can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.
- Healthcare providers ordering remdesivir in non-hospitalized patients must be fully familiar with the VEKLURY® (remdesivir) Dosing and Administration Guide[8], and the MDHHS Priority Eligibility Criteria for COVID-19 Outpatient Therapy (see Appendix A). Providers should assure that patients in higher priority tiers are treated prior to those prioritized lower.

Pediatric Considerations for Outpatient Remdesivir*

Outpatient remdesivir is now authorized by the FDA under an EUA for the treatment of COVID-19 in pediatric patients less than 12 years of age weighing 3.5 kg to less than 40 kg, with positive results of direct SARS-CoV-2 viral testing, and who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death[9].

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[6] EUA 046 Gilead Remdesivir LOA Outpatients (01212022) (fda.gov)

[7] Study to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting - Full Text View - ClinicalTrials.gov

[8] https://www.vekluryhcp.com/downloads/Dosing_and_Administration_Guide.pdf

[9] EUA 046 Gilead Remdesivir LOA Outpatients (01212022) (fda.gov)

The only authorized dosage form of remdesivir for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg is the remdesivir formulation supplied as 100 mg lyophilized powder in vial.

The recommended dosage for pediatric patients **weighing 3.5 kg to less than 40 kg** is a single loading dose of remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily from Day 2.

The recommended dosage for pediatric patients less than **12 years of age and weighing 40 kg and higher** is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2[10].

Further information can be found in the FDA EUA issued on January 21, 2022: EUA 046 Veklury (remdesivir) FS for HCPs (01212022) (fda.gov)

*General information on remdesivir can be found in Appendix D.

Evusheld for Pre-Exposure Prophylaxis in High-Risk Individuals**

Evusheld (tixagevimab/cilgavimab) is a long-acting mAb therapy intended for pre-exposure prophylaxis (PrEP) in individuals who are moderate to severely immunocompromised and those few who have had documented severe reactions to the COVID-19 vaccine. The medication is administered as two IM injections given every 6 months. This medication has been primarily provided to healthcare systems based on their reported volume of patients with a diagnosis of an immunocompromising condition. It is also available in limited quantities to independent hospitals and other healthcare providers not affiliated with a healthcare system administering Evusheld. Because of the limited supply, MDHHS has established a separate 2-tiered set of priority eligibility criteria for Evusheld that is consistent with NIH criteria[11] for this medication (see Appendix E). Patients in Tier 1 should receive the medication prior to those in Tier 2 when patients in both tiers are requesting the medication.

**Additional information on Evusheld, including the priority eligibility criteria, is included in Appendix E.

[10] EUA 046 Veklury (remdesivir) FS for HCPs (01212022) (fda.gov)

[11] Statement on Therapies for High-Risk, Nonhospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)

APPENDIX A

Priority Eligibility Criteria for COVID-19 Outpatient Therapy (Revised January 28, 2022)

Tier	Eligibility Criteria	Paxlovid PO	Sotrovimab[4] IV	Remdesivir IV	Molnupiravir PO
	Preference Per NIH Treatment Guidelines	→	→	→	→
	Treatment must be started within (X) days of symptoms:	5 days	10 days	7 days	5 days
	Availability:	**Limited Statewide** - Select Meijer - Select pharmacies - Select FQHCs - Select THCs	**Statewide** - Variable sites	**Statewide** -Variable sites	**Limited Statewide** - Select Meijer - Select pharmacies
1A	– Any age (per applicable EUA or FDA approval) with moderate to severe immunocompromise regardless of vaccine status **or** – Age ≥75 YO and not up to date on COVID vaccines[1]	**Yes**	**Yes**	**Yes**	Alternative[2]
1B	– Age 65-74 YO, not up to date on COVID vaccines[1], and with MI priority risk factor[3] – Pregnant and not up to date on COVID vaccines[1]	**Yes**	**Yes**	**Yes**	Alternative[2]
2	– Age 65-74 YO and not up to date on COVID vaccines[1] – Age <65 YO, not up to date on COVID vaccines[1]with MI priority risk factors[3]	**Yes**	**Yes[5]**	**Yes**	Alternative[2]
3A	– Age ≥75 YO and up to date on COVID vaccines[1] – Age 65-74 YO, up to date on COVID vaccines[1], and with MI priority risk factors[3]	**Yes**	Not currently eligible	Not currently eligible	Alternative[2]
3B	– Age 65-74 YO, up to date on COVID vaccines[1], and with CDC risk factors	Not currently eligible	Not currently eligible	Not currently eligible	**Yes**
4	– Age ≥65 YO and up to date on COVID vaccines[1] – Age <65 YO, up to date on COVID vaccines[1], and with CDC risk factors	Not currently eligible	Not currently eligible	Not currently eligible	**Yes**

mAb=monoclonal antibody, FQHC=Federally Qualified Health Centers, THC=Tribal Health Centers

1 Those not up to date include those who are not vaccinated, have not completed their initial series, and those not boosted, when eligible as per Stay Up to Date with Your Vaccines | CDC

2 Alternatives include Paxlovid, sotrovimab, and remdesivir that are available in a timely manner

3 MI priority risk factors include:

- Obesity (BMI ≥ 35)
- Chronic respiratory disease (e.g., COPD, moderate or severe asthma requires daily inhaled corticosteroid, bronchiectasis, CF, ILD)
- Pregnancy (Note: In pregnancy, molnupiravir should not be used and Paxlovid and remdesivir should be used with caution when sotrovimab is unavailable)
- Chronic Kidney Disease (stage III, IV, or end stage CKD-GFR) (special considerations with Paxlovid)
- Cardiovascular disease (e.g., HTN, valvular disease, CVA, PAD, CHF)
- Diabetes

4 Sotrovimab is currently the only mAb therapy active against the Omicron variant and is in limited supply. Other mAb products may be considered, if indicated.

5 Use in lower tiers should be done only when higher tiers are able to be treated in a timely manner. Higher tier patients are a priority.

APPENDIX B

Priority Eligibility Criteria and Prescribing for Paxlovid™

Prescribers must comply with requirements of the US Food and Drug Administration's FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID (fda.gov)™ and with the State of Michigan Priority Eligibility Criteria for this medication (Appendix A). Patients must have tested positive for SARS-CoV-2. PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (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, and
- who meet the current Priority Eligibility Criteria (see Appendix A)

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.

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.

Warning and Precautions

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.

Medication Interactions and Potential for Severe Adverse Events with PAXLOVID

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy.

Appendix C

Priority Eligibility Criteria and Prescribing for Molnupiravir

Prescribers must comply with requirements of the US Food and Drug Administration's FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR (fda.gov) and with the State of Michigan Priority Eligibility Criteria for this medication (Appendix A). 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, and
- who meet the current Priority Eligibility Criteria (see Appendix A)

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.

Appendix D
Remdesivir Administration to Non-Hospitalized Patients

Remdesivir Administration

Dose Reconstitution	**Dose Reconstitution**
Remdesivir for injection, 100 mg/vial, lyophilized powder must be reconstituted with 19 mL Sterile Waterfor 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

Remdesivir dose	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 reconstituted Remdesivir for injection
Loading dose200 mg (2 vials)	250 ml 100 ml	40 ml	40 ml (2 x 20 ml)
Maintenance dose100 mg (1 vial)	250 ml 100 ml	20 ml	20 ml

Dilution

Remdesivir dose	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 Remdesivirinjection
Loading dose 200 mg (2 vials)	250 ml	40ml	40 ml (2 x 20 ml)
Maintenance dose 100 mg (1 vial)		20 ml	20 ml

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 ml	30 minutes	8.33 ml/min
	60 minutes	4.17 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

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 ml	30 minutes	8.33 ml/min
	60 minutes	4.17 ml/min
	120 minutes	2.08 ml/min

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.

Appendix E
Evusheld for Pre-Exposure Prophylaxis

Allocation to Healthcare Systems

MDHHS has previously developed a process for the initial allocation of Evusheld to 17 Michigan healthcare systems. This was determined based on data received from the Michigan Health and Hospital Association (MHA) on the number of unique patients receiving inpatient or outpatient care with an associated diagnosis consistent with an immunocompromising condition. These data were used to proportionately allocate the medication between healthcare systems. Subsequent (anticipated) biweekly allocations will be adjusted based on the ability of the healthcare systems to use the medication based on priority tiers and available supply. Inability to use the medication may result in decreased future allocations.

Access to Independent Hospitals and Special Populations

Independent hospitals not affiliated with one of the 17 healthcare systems directly receiving shipments of medication will be able to request an allocation of medication after identifying the amount needed for their patient population that meets Evusheld criteria. This cache will also be used to serve other special populations (e.g., Michigan Department of Corrections) who have eligible patients meeting current priority tiers. Like the healthcare systems, those requesting medication from the MDHHS cache will be required to have in place scarce resource allocation processes that will allow fair and equitable access. Healthcare systems should make additional efforts to reach eligible patients who may be more difficult to contact and who may have barriers to communications.

Tiered Prioritization

As demand for this medication is likely to exceed supply, a two-tiered prioritization system has been developed to help assure those who are at higher risk receive priority access. The following tiered prioritization categories has been adapted from the NIH Treatment Panel Guidelines[12]. To assure fair and equitable access, this stratification will be used in allocating this medication in Michigan. Healthcare system scarce resource allocation (or similar) committees may further stratify within the second tier, as appropriate for their system.

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[12] National Institutes of Health. (2021, December 23). *Statement on patient prioritization for outpatient therapies*. NIH COVID-19 Patient Treatment Guidelines. Retrieved December 27, 2021, from https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/

Priority Criteria to Receive Evusheld (tixagevimab/cilgavimab) for Pre-Exposure Prophylaxis for COVID-19 in High-Risk Individuals
Tier 1 Criteria
a) Patients within 1 year of receiving B-cell depleting therapies (e.g., rituximab,ocrelizumab, ofatumumab, alemtuzumab) b) Patients receiving Bruton tyrosine kinase inhibitors c) Chimeric antigen receptor T cell recipients d) Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication e) Patients with hematologic malignancies who are on active therapy f) Solid-organ transplant recipients who: 1) are lung transplant recipients, or 2) are within 1 year of receiving a solid-organ transplant (other than lungtransplant), or 3) solid-organ transplant recipients with recent treatment for acute rejection withT or B cell depleting agents g) Patients with severe combined immunodeficiencies h) Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm i) Other patients with severe immunodeficiency to be reviewed on an individual basis by designated senior clinicians with no established physician obligation to the patient.
Tier 2 Criteria[2]
a) Patients with active treatment for solid tumor malignancies b) Patients with moderate or severe primary immunodeficiency (e.g., DiGeorgesyndrome, Wiskott-Aldrich syndrome) c) Advanced or untreated HIV infection (people with HIV and CD4 cell counts of 50-200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) d) Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive that are e) immunosuppressive or immunomodulatory (e.g., B-cell depleting agents), tumor-necrosis (TNF) blockers, and other biologic agents f) For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s)

Operationalizing Tiered Prioritization within Healthcare Systems

Recognizing the uniqueness of healthcare systems, it is understood that operationalizing access to Evusheld will be done in different ways within healthcare systems. It is also understood that this is a formative process that will need to be adapted and revised over time to best serve high-risk patients. Healthcare systems should consider the following, in consultation with their scarce resource allocation committees, in establishing policies for Evusheld administration to qualifying patients.

Establish Prioritization Criteria

To assure statewide equity and fairness in providing access to Evusheld in higher risk patients, healthcare systems should adopt the MDHHS Prioritization Criteria. Tier 1 Criteria are based on the NIH Treatment Panel Guidelines for prioritization of outpatient therapies. Patients meeting Tier 1 Criteria should receive Evusheld prior to those meeting Tier 2 Criteria. Healthcare systems may elect to further stratify Tier 1 and Tier 2 criteria to better address system needs and patient types. Given demand exceeding supply, systems may wish to further prioritize severely immunocompromised individuals over moderately immunocompromised individuals. It should be noted that this medication is not FDA-approved and therefore off-label ordering is not permitted under the EUA.

Identify and Screen Potentially Eligible Patients

Beginning with Tier 1, patients should be identified and screened who potentially meet the criteria. This can be accomplished through one or more processes including through an electronic medical record search for appropriate conditions or through direct referral from the patient's healthcare provider.

Patient Selection and Order of Administration

Using a list of identified and screened patients identified above, those meeting the criteria should be placed in the order to receive Evusheld.

Patient Contact and Counseling

Once patients are selected, they should be contacted by a qualified healthcare provider and counseled on the potential risks and benefits of Evusheld, in accordance with the Fact Sheet for Patients and Caregivers. Special attention should be provided to **those at high-risk for cardiovascular events** as described in the Fact Sheet. Patients wishing to receive Evusheld are required to receive the FDA's Fact Sheet for Patients and Caregivers prior to receiving the medication.

Order and Provide the Medication to the Site of Distribution and Schedule Appointment
Once patients have been selected and agree to receive Evusheld, an order should be provided by an authorized healthcare provider. The medication should be provided to the site of administration and an appointment should be scheduled.

Administer the Medication
The medication should be administered as directed by the FDA's Fact Sheet for Healthcare Providers and patients must be observed for at least 60 minutes after administration.

Complete Required State and Federal Reporting
All healthcare systems must complete, in a timely manner, all required federal and state reporting requirements. Failure to comply with this may jeopardize future allocations to healthcare systems and to the state.

Readminister Medication Every 6 Months
The current EUA calls for the re-administration of Evusheld every 6 months to sustain pre- exposure prophylaxis.

Monitor Safety and Effectiveness
Healthcare systems should monitor patients receiving Evusheld for safety and effectiveness in preventing COVID-19 infections, and especially hospitalizations or deaths.

Centralized or Decentralized Distribution
MDHHS will initially allocate Evusheld to one central receiving pharmacy for each healthcare system. Based on a variety of factors, healthcare systems may adopt a centralized, decentralized, or hybrid process for selection of patients and administration of medication. The selection process could occur centrally, but the medication should be administered at multiple sites. Alternatively, healthcare systems could adopt a more decentralized approach in which multiple sites serving specific geographic areas (e.g., norther region) or populations (e.g., the oncology clinic).

Medication may be redistributed to various sites, clinics, etc. as needed to best serve patients.

Redistribution Between Healthcare Systems
In the event a healthcare system is underusing Evusheld, inventory assigned to that healthcare system may be redistributed to other healthcare systems who are in need.