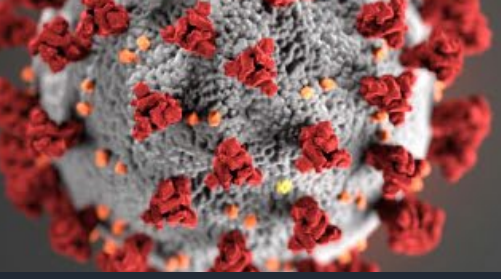

Off-Label Use of Remdesivir for the Treatment of Mild to Moderate COVID-19 in Non-Hospitalized High-Risk Patients

January 19, 2022

Recommendation

Consistent with the current National Institutes of Health (NIH) Treatment Guidelines[1], for non-hospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression (see below), the use of Remdesivir 200 mg IV administered on Day 1, followed by remdesivir 100 mg IV daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg is an appropriate therapy, especially when other authorized therapies are not readily available.

Background

Monoclonal Antibodies: Since November 2020, monoclonal antibody (mAb) therapy has been a safe and highly effective treatment for high-risk individuals who are experiencing mild-to-moderately severe COVID-19. There are currently three mAb therapies that have received an Emergency Use Authorization (EUA) from the US Food and Drug Administration: bamlanivimab/etesevimab, casirivimab/imdevimab (REGEN-COV); and sotrovimab. However, only sotrovimab has demonstrated laboratory effectiveness against the Omicron variant of the SARS-CoV-2 virus. Sotrovimab is currently in short supply and must be administered as a one-time IV infusion, making timely access to this medication challenging.

Oral Anti-Virals*:* Recently, the oral antiviral medications PAXLOVID and molnupiravir were granted EUAs by the FDA for the outpatient treatment of mild to moderate COVID-19 in high-risk patients. These medications must be started within 5 days of symptoms and are taken twice daily for 5 days.

- Paxlovid, a protease inhibitor, is currently preferred by the NIH for the treatment of mild to moderate COVID-19 in high-risk, non-hospitalized patients. Paxlovid consists of nirmatrelvir co-administered with ritonavir which is required to increase concentrations to the target therapeutic ranges. Paxlovid has demonstrated antiviral activity against all coronaviruses that are known to infect humans. In the EPIC-HR Study, patients receiving Paxlovid within 5 days of symptom onset experienced an 86% relative risk reduction in hospitalization or death compared to those treated with placebo (-5.62% estimated absolute reduction; 95% CI, -7.21% to -4.03%; $P < 0.0001$).[2]
- Molnupiravir is a ribonucleoside that has potent antiviral activity against SARS-CoV-2.[3] As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. For these, and other reasons, the FDA and MDHHS, have limited the use of this medication to patients in which other therapies are not available. [4]

Because of the limited availability of sotrovimab and Paxlovid and, given the continued high degree of COVID-19 activity in Michigan, it is important that other safe and effective therapies be pursued.

Off-Label Use of 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.[1] As Omicron becomes 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 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),[5] 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 currently approved by the FDA for use in hospitalized individuals, and outpatient treatment would be an off-label indication.
- 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.

Clinical Guidance in the Use of Remdesivir in Non-Hospitalized Patients

Healthcare providers ordering remdesivir in non-hospitalized patients must be fully familiar with the VEKLURY® (remdesivir) Dosing and Administration Guide[6], NIH Treatment Guidelines[1], and any EUA that may be issued by the FDA. See Appendix A for a brief summary on information regarding administration.

High-Risk Patients and Patient Prioritization

Currently, mAb and oral antiviral medications are limited by the FDA EUA for use in patients who have conditions that are associated with higher risk of disease progression leading to hospitalization or death.[v] However, given the shortage of effective therapeutics, MDHHS has adopted a 4-tiered Priority Eligibility Criteria for COVID-19 Outpatient Therapy (See Appendix B) that includes more restrictive priority risk factors as specified below:

- Obesity (BMI $\geq$ 35)
- Chronic respiratory disease (e.g., COPD, moderate or severe asthma, bronchiectasis, CF, ILD)
- Pregnancy (cautiously consider remdesivir when sotrovimab is unavailable)
- Chronic Kidney Disease (remdesivir not recommended in patients with eGFR <30 mL/min)
- Cardiovascular disease (e.g., HTN, valvular disease, CVA, PAD, CHF)
- Diabetes

Providers should assure that patients in higher priority tiers are treated prior to those prioritized lower.

APPENDIX A – Remdesivir Administration to Non-Hospitalized Patients

<table>
<tr><th colspan="8">Remdesivir Administration[vi]</th></tr>
<tr><th colspan="4">Dose Reconstitution</th><th colspan="4">Dose Reconstitution</th></tr>
<tr><td colspan="4">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</td><td colspan="4">Remdesivir injection, 100 mg/20 mL (5 mg/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</td></tr>
<tr><th colspan="4">Dilution</th><th colspan="4">Dilution</th></tr>
<tr><td>Remdesivir dose</td><td>0.9% sodium chloride infusion bag volume to be used</td><td>Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag</td><td>Required volume of reconstituted Remdesivir for injection</td><td>Remdesivir dose</td><td>0.9% sodium chloride infusion bag volume to be used</td><td>Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag</td><td>Required volume of Remdesivir injection</td></tr>
<tr><td>Loading dose 200 mg (2 vials)</td><td>250 ml
100 ml</td><td>40 ml</td><td>40 ml (2 x 20 ml)</td><td>Loading dose 200 mg (2 vials)</td><td rowspan="2">250 ml</td><td>40ml</td><td>40 ml (2 x 20 ml)</td></tr>
<tr><td>Maintenance dose 100 mg (1 vial)</td><td>250 ml
100 ml</td><td>20 ml</td><td>20 ml</td><td>Maintenance dose 100 mg (1 vial)</td><td>20 ml</td><td>20 ml</td></tr>
<tr><td colspan="2">Infusion Bag Volume</td><td>Infusion Time</td><td>Rate of Infusion</td><td colspan="2">Infusion Bag Volume</td><td>Infusion Time</td><td>Rate of Infusion</td></tr>
<tr><td colspan="2" rowspan="3">250 ml</td><td>30 minutes</td><td>8.33 ml/min</td><td colspan="2" rowspan="6">250 ml</td><td>30 minutes</td><td>8.33 ml/min</td></tr>
<tr><td>60 minutes</td><td>4.17 ml/min</td><td>60 minutes</td><td>4.17 ml/min</td></tr>
<tr><td>120 minutes</td><td>2.08 ml/min</td><td>120 minutes</td><td>2.08 ml/min</td></tr>
<tr><td colspan="2" rowspan="3">100 ml</td><td>30 minutes</td><td>3.33 ml/min</td></tr>
<tr><td>60 minutes</td><td>1.67 ml/min</td></tr>
<tr><td>120 minutes</td><td>0.83 ml/min</td></tr>
<tr><td colspan="8">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</td></tr>
</table>

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 B – Priority Eligibility Criteria for COVID-19 Outpatient Therapy

Priority Eligibility Criteria for COVID-19 Outpatient Therapy (Revised January 19, 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 • Selected FQHCs • Selected 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 with COVID vaccines[1]	**Yes**	**Yes**	**Yes**	Alternative[2]
1B	• Age 65-74 YO, not up to date with COVID vaccines[1], and with MI priority risk factor[3] • Pregnant and not up to date with COVID vaccines[1]	**Yes**	**Yes**	**Yes**	Alternative[2]
2	• Age 65-74 YO and not up to date with COVID vaccines[1] • Age <65 YO, not up to date with COVID vaccines[1] with MI priority factors[3]	**Yes**	**Yes[5]**	**Yes**	Alternative[2]
3A	• Age ≥75 YO and up to date with COVID vaccines[1] • Age 65-74 YO, up to date with COVID vaccines[1], and with MI priority risk factors[3]	Not currently eligible	Not currently eligible	Not currently eligible	**Yes**
3B	• Age 65-74 YO, up to date with COVID vaccines[1], and with CDC risk factors	Not currently eligible	Not currently eligible	Not currently eligible	Not currently eligible
4	• Age ≥65 YO and up to date with COVID vaccines[1] • Age <65 YO, up to date with COVID vaccines[1], and with CDC risk factors	Not currently eligible	Not currently eligible	Not currently eligible	Not currently eligible

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, 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.

References

[1]. National Institutes of Health. The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Non-hospitalized Patients with Mild to Moderate COVID-19. 2021. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2021. Available at: https://www.fda.gov/media/155050/download.

[3]. Zhou S, Hill CS, Sarkar S, et al. Beta-d-N4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. *J Infect Dis*. 2021;224(3):415-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33961695.

[4]. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. 2021. Available at: https://www.fda.gov/media/155054/download

[5]. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers, 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

[6]. VEKLURY® (remdesivir) Dosing and Administration Guide. 2021. Available from: https://www.vekluryhcp.com/downloads/Dosing_and_Administration_Guide.pdf

APPENDIX C – Billing Codes for Remdesivir Outpatient Therapy

Remdesivir is currently available for purchase from pharmaceutical supply companies (AmerisourceBergen Contact Us | AmerisourceBergen). This medication will not be provided by the federal government or the State of Michigan. Following the recent statement from the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel regarding therapies for the COVID-19 Omicron variant, CMS created HCPCS code J0248 for VEKLURY™ (remdesivir) antiviral medication when administered in an outpatient setting. This code is available for use by all payers and is effective for dates of service on or after December 23, 2021:

- Long descriptor: Injection, remdesivir, 1 mg
- Short descriptor: Inj, remdesivir, 1 mg

Medicare Administrative Contractors (MACs) determine Medicare coverage when there is no national coverage determination, including in cases when providers use FDA-approved drugs for indications other than what is on the approved label. The MACs consider the major drug compendia, authoritative medical literature and accepted standards of medical practice to determine medical necessity when considering coverage. Therefore, the MACs will determine Medicare coverage for HCPCS code J0248 for VEKLURY™ (remdesivir) administered in an outpatient setting. Your MAC will share coverage and claims processing information for J0248. Contact your MAC if you have questions about coverage. (2022-01-07-MLNC-SE | CMS)