FORMULARY MONOGRAPH

Remdesivir (VEKLURY®)
[Gilead Sciences, Inc.]

REQUEST

No formal request has been made to date for formulary review

THERAPEUTIC USE[1]

- Drug Class: Antiviral
- Population Served: Adult and pediatric patients (12 years of age and older weighing at least 40 kg)

BACKGROUND

- Based on favorable initial data from a National Institute of Allergy and Infectious Diseases (NIAID) sponsored randomized double-blind clinical trial, Remdesivir was granted an emergency use authorization (EUA) for the treatment of COVID-19 on May 1, 2020.[4,5]
- On October 22, 2020 Remdesivir was approved by the Food and Drug Administration for the treatment of hospitalized patients with COVID-19 and is the only FDA-approved treatment currently available.[1]
- The Infectious Diseases Society of America (IDSA) guidelines for the management of COVID-19 suggest using remdesivir over no antiviral treatment for the management of patients with severe COVID-19 requiring supplemental oxygen, mechanical ventilation or ECMO (conditional recommendation, low certainty of evidence). The guidelines acknowledge that remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.[2]
- The National Institute of Health guidelines for the management of COVID-19 recommended the use of remdesivir in hospitalized patients with COVID-19 who require low-flow supplemental oxygen as an AI recommendation, high-flow/noninvasive ventilation as an AIII recommendation, and mechanical ventilation/ECMO as a CIII recommendation.[3]

CLINICAL PHARMACOLOGY and MECHANISM OF ACTION[1]

Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that is metabolized to the pharmacologically active nucleoside triphosphate metabolite after being distributed into cells. Remdesivir triphosphate acts as an adenosine triphosphate analog and competes for incorporation into RNA chains by the SARS-CoV-2 RdRp, resulting in chain termination and inhibition of viral replication.

FDA APPROVED INDICATIONS[1]

- Treatment of Coronavirus Disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) requiring hospitalization

POTENTIAL UNLABELED USE / OFF LABEL USE

- None

Subcommittee (s) Reviewers	PHHS PROPOSED Indications for Use	Literature to Support Off Label Proposed Indications
Nikki Mai, PharmD Jessica Ortwine, PharmD Wenjing Wei, PharmD Norman Mang, PharmD Bonnie Prokesch, MD	FDA indications meeting PHHS criteria for use	N/A

PROCUREMENT & STORAGE[1]

Formulation	Storage
Injection (5 mg/mL solution)	Store at refrigerated temperature (2°C to 8°C [36°F to 46°F])
Lyophilized powder	Store vials below 30°C (below 86°F)

Once diluted for infusion, may store for no more than 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F])

HAZARDOUS CLASSIFICATION

- Non-hazardous

DOSAGE & ADMINISTRATION[1]

Formulation	Dosage	Administration
Injection (5 mg/mL solution)	200 mg x 1, then 100 mg daily	• Dilute solution in 250 mL 0.9% sodium chloride • Administer over 30-120 minutes
Lyophilized powder		• Dilute 100 mg with 19 mL sterile water • Dilute reconstituted solution with 100 mL or 250 mL 0.9% sodium chloride • Administer over 30-120 minutes

(Table below is for Epic Willow build)

Order Build Elements:	IT Build Notes (use N/A where necessary):
Name and strength of all units needing to be built for dispensation	Remdesivir 200 mg in sodium chloride 0.9% 250 mL IVPB Remdesivir 100 mg in sodium chloride 0.9% 250 mL IVPB
Default Dose	200 mg, 100 mg
Dose Buttons	200 mg, 100 mg
How should doses be rounded? (1, 0.1,	N/A

0.01 to the nearest mcg, mg, etc…)	
Should the oral dosage form in Epic be built with the ability to order half doses ie: are half tablet doses clinically relevant?	N/A
Available Routes (this allows IT to exclude routes in look up not appropriate for use)	Intravenous
Default Route	Intravenous
Route Buttons (Radial Buttons to add)	Intravenous only
Default Frequency	Every 24 hours
Frequency Buttons	Every 24 hours only
PRN Reasons	N/A
Default Duration	60 minutes
Duration Buttons	60 minutes
Comments- Pharmacy notes	N/A
MAR Administration Instructions	Can be infused over 30 minutes or 120 minutes if needed
Order Instructions	N/A
Label Comments	N/A
Proportion of Days Covered (PDC) Class	N/A

IV GUIDELINE MONOGRAPH TEMPLATE

DRUG	APPROVED NURSING AREA (s)	IV PUSH (Yes/No)	INTERMITTENT INFUSION (Yes/No)	CONTINUOUS INFUSION (Yes/No)	INFUSION PUMP REQUIRED (Yes/No)	REFERENCE	ADDITIONAL INFORMATION
Remdesivir	Any	No	Yes	No	Yes	Package Insert	Administer as an IV infusion over 30-120 minutes.

Dose	Recommended Diluent	Volume	Rate
200 mg (loading)	NS	250 mL	Over 30 – 120 min
100 mg (maintenance)	NS	250 mL	Over 30 – 120 min

PHARMACOKINETICS[1]

Metabolism	CES1 (80%), Cathepsin A (10%), CYP3A4 (10%)
Bioavailability	N/A
Elimination	• Metabolism (only 10% of remdesivir dose excreted in urine) • Metabolites GS-441524 and GS-704277 have 49% and 3% urinary excretion, respectively
Half life (t 1/2)	1 hour

PHARMACOKINETICS IN SPECIAL POPULATIONS[1]

Special Population	Systemic Availability
Gender (females)	• Not evaluated
Elderly - **age** > **65 years**	• Not evaluated
Pediatric - age <18 years	• Not evaluated • Use in pediatric patients ≥ 12 years and ≥ 40 kg is based on extrapolation of pediatric efficacy from adequate and well-controlled studies in adults
Renal Impairment	• Not evaluated • Package insert: Not recommended in patients with eGFR < 30 mL/min due to formulation with betadex sulfobutyl ether sodium (SBECD) • Expert opinion: Significant toxicity with a short duration of therapy (e.g., 5 to 10 days) is unlikely. Benefits may outweigh the risks in select patients.[6,7]
Hepatic Impairment (Moderate Impairment)	• Not evaluated

PREGNANCY SUMMARY & USE IN BREAST FEEDING[1]

- Pregnancy: Available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.
- Lactation: There are no available data on the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. Remdesivir and its metabolites were detected in the plasma of nursing rat pups at exposures that were approximately 1% that of maternal exposure on Lactation Day 10 after administration to pregnant rats from Gestation Day 6 to Lactation Day 20.

ADVERSE DRUG EVENTS / EFFECTS[1]

- Hypersensitivity including infusion-related and anaphylactic reactions
- Increased risk of transaminase elevations

CONTRAINDICATIONS[1]

- History of clinically significant hypersensitivity reactions to remdesivir or any components of the product

MEDICATION SAFETY ASSESSMENT & RECOMMENDATIONS[1]

- **Black box Warnings**: None
- **Sentinel Events Advisories posted**: None
- **High Alert/SALAD**: None
- **Dual Sign/Witness**: None

- **Monitoring**:
    - Perform renal function, hepatic function, and prothrombin monitoring at baseline and as clinically appropriate during therapy
    - Monitor for signs/symptoms of infusion reaction
- **Significant Drug Interactions**:
    - Concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate may diminish therapeutic effect of remdesivir
    - Remdesivir and its metabolites are substrates for CYP3A4, OATP1B1, OATP1B3, P-glycoprotein transporters, and MATE1. The clinical relevance of these in vitro assessments has not been established.
- **REMS requirements**: None
- **Warnings and Precautions**
    - Hypersensitivity including infusion-related and anaphylactic reactions
    - Increased risk of transaminase elevations
    - Risk of reduced antiviral activity when co-administered with chloroquine phosphate or hydroxychloroquine sulfate
- **Potential for Errors and Abuse**: None
- **Other Risks**: None

SIMILAR PRODUCTS BY CLASS or TREATMENT INDICATION

Available Products	Indications
N/A	**N/A**

THERAPEUTIC EFFECTIVENESS

See written summary of clinical trials in Summary/Recommendation section below

Citation	Design*	Study Population	Outcomes	Critique & Interpretation
Wang; Lancet 2020.[8]	Randomized, double-blind, placebo-controlled, multicenter clinical trial. • Remdesivir x 10 days (n = 158) • Placebo x 10 days (n = 78)	• Age ≥ 18 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO_2 ≤ 94% on room air or PaO_2/FiO_2 ≤ 300 • Symptomatic ≤ 12 days • ALT or AST < 5x ULN • eGFR > 30 mL/min	No difference in time to clinical improvement: • Remdesivir 21 days vs. placebo 23 days; HR 1.23 (95% CI 0.87-1.75) • Symptoms ≤ 10 days: 18 days vs. 23 days; HR 1.52 (0.95-2.43) No difference in 28-day mortality: • Remdesivir 22/158 (14%) vs. placebo 10/78 (13%) No difference in duration of hospital admission: • Remdesivir 25 days vs. placebo 24 days No difference in viral load reduction Incidence of adverse events similar between groups • Low rates of transaminitis overall • Only 1% discontinued Remdesivir due to ALT elevation	Strengths: • Randomized controlled trial • Low loss to follow-up • Evaluated SARS-CoV-2 viral load Limitations: • Did not complete enrollment due to control of the outbreak resulting in low power for the study Interpretation: • Results are inconclusive given that the study was underpowered

Beigel; NEJM 2020.[9]
 	
(ACTT-1)
	Randomized, double-blind, placebo-controlled clinical trial of hospitalized adult subjects with mild, moderate, or severe COVID-19.
	• Remdesivir x 10 days (n = 541)
	• Placebo x 10 days (n = 521)
		• Age ≥ 18 years
		• Positive SARS-CoV-2 PCR
		• Radiographic evidence of pulmonary infiltrates
		• SpO_2 ≤ 94% on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO
		• ALT or AST < 5x ULN
		• eGFR > 30 mL/min
			Remdesivir associated with significantly shorter recovery time by day 29:
			• Remdesivir 10 days vs. placebo 15 days; RR 1.29 (95% CI 1.12 – 1.49; P<0.001)
			  ○ Symptoms ≤ 10d: RR 1.37 (1.14-1.64)
			  ○ Receiving O_2: RR 1.45 (1.18-1.79)
			
			No difference in incidence of serious adverse events
				Strengths:
				• Adequate power
				• High protocol adherence
				
				Limitations:
				• Did not evaluate SARS-CoV-2 viral load
				
				Interpretation:
				• Remdesivir is effective at improving clinical recovery in COVID-19 patients. Remdesivir may be beneficial in preventing progression to more severe respiratory disease and its benefit is most apparent in those requiring supplemental oxygen.

Goldman; NEJM 2020.[10] (SIMPLE Severe)	Randomized, open-label multicenter clinical trial. • Remdesivir x 5 days (n = 200) • Remdesivir x 10 days (n = 197)	• Age ≥ 12 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO_2 ≤ 94% on room air or requiring supplemental oxygen • ALT or AST < 5x ULN • eGFR > 30 mL/min	No significant difference in clinical improvement between 5 vs. 10 days Among patients receiving non-invasive ventilation or high-flow oxygen on day 5, day-14 mortality was 10% in 5-day group vs. 15% in 10-day group. Among patients receiving mechanical ventilation or ECMO on day 5, day-14 mortality was 40% in 5-day group vs. 17% in 10-day group.	Strengths: • First study to evaluate optimal duration of remdesivir in COVID19 • Adequate power • No placebo control Limitations: • Did not evaluate SARS-CoV-2 viral load • Excluded patients on mechanical ventilation or ECMO Interpretation: • 5 days of remdesivir is sufficient to treat COVID-19

				patients who are not receiving mechanical ventilation/ECMO. Patients who progress to mechanical ventilation or ECMO may benefit from a 10 day course.
Spinner; JAMA 2020.[11] (SIMPLE Moderate)	Randomized, open-label multicenter clinical trial. • Remdesivir x 5 days (n = 191) • Remdesivir x 10 days (n = 193) • Standard of care (SOC) (n = 200)	• Age ≥ 12 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO_2 > 94% and breathing on room air at screening • ALT or AST < 5x ULN • eGFR > 50 mL/min	5-day course of Remdesivir associated with statistically significantly higher odds of having a better clinical status on day 11 compared to SOC, but not 10-day course: • 5-day vs. SOC: OR 1.65 (95% CI 1.09-2.48; P=0.02) • 10-day vs. SOC; OR 1.31 (95% CI 0.8-1.95; P=0.18)	Strengths: • First study to evaluate remdesivir in patients with moderate COVID-19 pneumonia; had adequate power Limitations: • Difference in outcome of uncertain clinical significance • Did not evaluate SARS-CoV-2 viral-loads • Did not stratify by sites, which could have influenced the results given the differences in patient care and discharge practices Interpretation: • A 5-day course of remdesivir may be sufficient to treat patients with moderate COVID-19 pneumonia
Pan; MedRxiv 2020.[12] (SOLIDARITY, prelim report)	Adaptive, randomized, open-label comparative trial. • Remdesivir x 10 days (n = 2,743) • Standard of care (SOC) (n = 2,708)	• Age ≥ 18 years • Diagnosis of Definitive COVID-19	Remdesivir not associated with reduction in in-hospital mortality compared to SOC: • Remdesivir 11% vs. SOC 12%; RR 0.95 (95% CI 0.81-1.11; P=0.50) Remdesivir not associated with reduced progression to mechanical ventilation • Remdesivir 11.9% vs SOC 11.5% Remdesivir not associated with reduced hospital length of stay (proportion of patients still admitted): • Day 7 – remdesivir 69% vs. SOC 59% • Day 14 – remdesivir 22% vs. SOC 19% • Day 21 – remdesivir 9% vs. SOC 8%	Strengths: • Large sample size Limitations: • Open-label study • No definition of COVID-19 or definitive COVID-19 • Did not stratify by oxygen requirements or site • Has not reported duration of symptoms prior to start of treatment • Inclusion criteria not clearly defined • Patients who are discharged were not followed • Did not use WHO ordinal scale Interpretation: • Remdesivir was not associated with improved in-hospital mortality among patients hospitalized with COVID-19

*Remdesivir treatment regimen was 200 mg IV on day 1 followed by 100 mg IV daily in all listed studies

ALT: alanine aminotransferase
AST: aspartate aminotransferase
ULN: upper limit of normal
eGFR: estimated glomerular filtration rate
SOC: standard of care

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VALUE ANALYSIS/ FINANCIAL ANALYSIS OF COST OF THERAPY

Treatment Regimen	Cost	Cost per Course	Estimated Cost per Year
Remdesivir 200 mg IV on day 1 followed by 100 mg IV daily for total 5-10 days	$520.00 per vial*	$3,120 – $5,720	Est. 20 vials/day: $3,600,000

*Wholesale acquisition cost (WAC)

Month (2020)	Vials purchased	PHHS Cost
July	920	$478,000
August	880	$457,600
September	560	$291,200
Total expense to date		**$1,226,000**

OVERALL SUMMARY AND RECOMMENDATION

Currently, remdesivir is the only FDA-approved treatment for COVID-19 in hospitalized patients. Conflicting data have been published regarding the clinical benefits of remdesivir and no clinical trials to date have shown a mortality benefit. The randomized, double-blind ACTT-1 trial demonstrated a significantly faster time to recovery among all patients receiving remdesivir compared to placebo, with the benefit most pronounced among patients either not receiving oxygen or receiving low-flow oxygen; however, the study was not powered to detect clinically significant differences in these subpopulations. The SIMPLE Moderate trial, which evaluated 5- and 10-day courses of remdesivir compared to standard of care therapy in patients not requiring supplemental oxygenation, showed significantly higher odds of improved clinical status in patients receiving the 5-day course, but this difference, interestingly, was not observed among patients receiving the 10-day course. The SIMPLE Severe trial found no difference overall between a 5-day and 10-day treatment course in patients with $SpO_2 \leq 94\%$ on room air or supplemental oxygen. Patients on mechanical ventilation or ECMO at baseline were excluded from this study; however, mortality among patients who progressed to requiring either of these interventions by day 5 was numerically higher in the 5-day group (40% vs. 17%). Conversely, both the study by Wang et al. as well as the World Health Organization-sponsored SOLIDARITY trial failed to show any benefit in duration of hospitalization, clinical improvement or progression of disease to mechanical ventilation in patients receiving remdesivir compared to placebo or standard of care.

While the true clinical benefit of remdesivir remains controversial, the low risk for adverse events coupled with its FDA approval status make it an appealing potential option for the treatment of COVID-19 from a risk/benefit standpoint. However, at an institutional cost of $3,120 – $5,720 per treatment course, the cost/benefit ratio must be taken into consideration. The daily usage of remdesivir fluctuates between 10 and 40 vials per day, depending on COVID-19 patient hospital census and community surges. To date, Parkland has purchased 2360 vials at a cost of $1.2 million which are estimated to last through the end of November. The extrapolated cost of remdesivir, using our current restrictions, is $3.6 million, but this cost will be significantly higher if Parkland restrictions are expanded to match those of the FDA approval criteria.

Based on current clinical trial results and internal data, remdesivir treatment is likely to be most effective when administered earlier in the disease course. However, we do not recommend giving this therapy to all hospitalized patients with COVID-19, as the majority of

patients with non-severe disease will recover without medical intervention. Taking into consideration the risk for disease progression and adverse effects, potential clinical benefit, significant institutional costs, as well as the IDSA and NIH guideline recommendations we recommend against administering remdesivir to all admitted patients with COVID-19. We recommend reserving remdesivir for use in the following patient populations:

- Laboratory-confirmed COVID-19 (by RT-PCR testing on a respiratory specimen) who are not already on remdesivir (e.g., for clinical trials or compassionate use)
- Any low flow supplemental oxygen requirement (patients requiring supplemental oxygen via high flow nasal cannula, bipap, or CPAP will be assessed by Antimicrobial Stewardship team on a case-by-case basis)
- Worsening clinical trajectory
- LFTs <10x ULN

In addition, all treatment courses of remdesivir will be limited to 5 days.

The enforcement of numerous restriction criteria would result in a significantly increased review burden on the staff pharmacists responsible for verifying orders of formulary medications. Additionally, the above restriction criteria delve into the nuances of the available clinical trial data. Because of the paucity of consistent data, the rate at which new data is being released, as well as on-going research regarding use of this agent in combination with other therapies, we do not feel it is a reasonable expectation for staff pharmacists to be able to speak at an expert level on the use of remdesivir. This type of discussion is often required when orders do not meet restriction criteria. As such, we recommend keeping remdesivir as a non-formulary medication for the time being with all requests continuing to be reviewed by the Antimicrobial Stewardship pharmacist or physician chair prior to approval.

MONOGRAPH PREPARED BY AND DATE

Nikki Mai/Jessica Ortwine/Wenjing Wei/Norman Mang

November 10, 2020

*The Joint Commission Requirements MM.02.01.01 & CMS §482.25(b)(9)
(must be completed for each new drug addition)
MM.02.01.01

EP2. The hospital develops and approves criteria for selecting medications, which, at a minimum, include the following: - Indications for use - Effectiveness - Drug interactions - Potential for errors and abuse - Adverse drug events - Sentinel event advisories - Population(s) served (for example, pediatrics, geriatrics) - Other risks – Costs. The hospital determines a method to monitor the response of the patient.

Interpretive Guidelines §482.25(b)(9)

The medical staff must establish a formulary system. The formulary lists medications for dispensing or administration that the hospital maintains or that are readily available. In accordance with accepted standards of practice, the medical staff, in consultation with the pharmacy service, should develop written criteria for determining what medications are available for dispensing or administration. At a minimum, the criteria include the indication for use, effectiveness, risks (including propensity for medication errors, abuse potential, and sentinel events), and costs.

Processes and mechanisms should be established to monitor patient responses to a newly added medication before the medication is made available for dispensing or administration within the hospital.

REFERENCES

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