LRI Children's Hospital

Process for Remdesivir use in children under 4 weeks of age and 3kg

Staff relevant to:	UHL Children's Hospital staff treating Children under 4 weeks of age and 3 kg presenting with COVID pneumonia.
Team approval date: AWP approval date:	Dec 2022 Jan 2023
Original Version Written: Version:	19/11/20 5
Revision due:	January 2026
Written by: Reviewed by:	D Harris D Harris
Trust Ref:	C51/2021

Must be used in conjunction with latest RCPCH/UHL COVID guidelines

https://www.rcpch.ac.uk/resources/covid-19-clinical-management-children-admitted-hospital-suspected-covid-19

Contents

1. Introduction and Who Guideline applies to

NHSE advice recommends use in conjunction with dexamethasone in paediatric patients with confirmed severe COVID-19 and may consider use in patients with confirmed critical COVID-19; remdesivir is not recommended for patients with mild to moderate disease (NHSECommissioning, 2020)

Note: All patients aged over 4 weeks CGA and weigh at least 3 kg are provided treatment using the interim clinical guidance from NHSE (28 November 2022), including a Blueteq approval (NHSECommissioning, 2020) – speak to your pharmacist for more information

Use in children aged under 4 weeks and under 3kg

While remdesivir efficacy has been demonstrated in adults being treated for COVID-19, data in paediatric patients are limited (Chiotos K, 2020). The role of remdesivir in the treatment of COVID-19 in paediatric patients is still evolving. It is a virustatic agent, not virucidal, reliant on host immune clearance.

All candidates under the age of 4 weeks and 3 kg for treatment must be discussed with at least 2 members of the MDT - Dr Srini Bandi, Dr Julian Tang, Corrine Ashton and David Harris.

2. Guideline Standards and Procedures

There is no UK trial so all stock is supplied to the pharmacy on a per patient compassionate use request from the company, Gilead Pharmaceuticals, by the treating consultant. New stock must be requested for each new treatment

Patient Selection (NHSECommissioning, 2020)

Eligible patients must

- Be hospitalised with COVID pneumonia requiring supplemental oxygen and/or is severely immunocompromised
- Have renal function Creatinine Clearance > 30ml/min/1.73m^2
- Have ALT below 5 times the upper normal value
- Require Remdesivir within 10 days of onset of symptoms
- Have maximum treatment of 5 days
- Consent by parent/guardian to use off label treatment with limited data in of its use, efficacy and side effects
- Have a full approval from Gilead

Please discuss any potential cases with the MDT as early as possible in the admission to avoid out of hours supply as this may not be possible. This guideline should be followed at weekends and only overnight in cases of extreme urgency.

Requesting Stock

Compassionate Access Programme website - https://rdvcu.gilead.com/

Please refer to https://rdvcu.gilead.com/ for the current criteria and case submission. Please read the criteria carefully as these may have changed since your last submission.

Details required to complete the submission

Shipping address/details

- Pharmacy Stores Gate 9 Havelock Street, Leicester Royal Infirmary LEICESTER LE1 5WW

Contact names

LRI - David Harris (07939 051902) (david.harris@uhl-tr.nhs.uk) and Mohammed Karolia (0116 258 4465) (Pharmacy.purchasing@uhl-tr.nhs.uk) (Consider adding the name of the lead pharmacist for the relevant ward too)

Patient Information

- Patient initials, date of birth, brief clinical course, gender, current clinical status, imaging results and pertinent physical exam/vital signs inc weight and current oxygen requirements
- Most recent Urea, creatinine, estimated Creatinine clearance, ALT, AST, ALP, Total Bilirubin
- PCR status, pregnancy status, need for mechanical ventilation, ECMO or pressor support, dialysis/CVVH status, brief PMH

Process

1. Submit request and await the initial confirmation email. Each case must be discussed with MDT as early as possible to obtain necessary approvals and stock in a timely manner, mainly to ensure the company are aware and will look out for the request
2. The requestor will receive an email some time later (not instant) with a provisional agreement pending return of the signed physician agreement. The requestor will also receive
    - Access to and details of the CRF that must be completed daily to have early access to the treatment – failure to complete may prevent future access to the drug for yourself of other UHL colleagues
    - Informed consent template – to be used in addition to the trust consent document as this is a treatment still under investigation
    - Latest Investigator protocol
    - Latest Pharmacy manual

- Latest Investigator brochure

3. Requestor must complete the physician agreement (all 22 pages) and reply back to the Gilead email to retain the patient reference if multiple cases are being requested; also cc'd to David Harris, relevant unit pharmacist and Mohammed Karolia. Do not send patient consent forms.
4. An email with final approval will be received on successful completion of this step permitting stock can be released by pharmacy – forward this the pharmacist to order the medication

Ordering stock from pharmacy

Contact pharmacy once final approval email has been received, consent obtained and the treatment has been prescribed. The pharmacist will require a copy of the final Gilead approval email and confirmation of consent to order stock.

Pharmacy

- Ordering pharmacist to email Pharmacy Purchasing team to create an order for the incoming (replacement) Remdesivir Paed FOC stock
- Stock will arrive addressed for the pharmacist, who will complete and return the Drug Shipment Note, and add the order number to the document.
- Stores team to receive the order into stock and place it in the Unlicensed Medicines location in the pharmacy for release via Pharmacy SOP 701 – Checking quality of unlicensed medicines
- Dispensary team to book out and supply Remdesivir Paed FOC stock from Unlicensed medicines area to the ward

Prescribing and dosing

Must not be given with lopinivir/ritonavir, chloroquine or hydroxychloroquine

There are 7 major drug interactions (listed below) for which co-administration is not recommended due to a potential reduction in Remedesivir concentrations.

Rifampicin	Rifapentine	Carbamazepine	Phenobarbital
Phenytoin	Primidone	St John's Wort	

Co-administration of drugs with Remdesivir has generally not been studied and recommendations related to drug interactions is based on theoretical data for the effects on metabolising enzymes - https://www.covid19-druginteractions.org/checker

PRETERM Neonates and Infants <56 Days of age (GileadSciencesInc, Personal Communication, 2020)

Day 1 IV	loading dose	2.5mg/kg daily
Days 2-5	maintenance dose	1.25mg/kg daily

Minimal data in this population, and PK is currently being studied/safety confirmed in our Pediatric Study Plan.

TERM Neonates and Infants <14 Days of age (GileadSciencesInc, Personal Communication, 2020)

Day 1 IV	loading dose	2.5mg/kg daily
Days 2-5	maintenance dose	1.25mg/kg daily

TERM ≥14 days of age with body weight ≥ 2.5 kg and < 40 kg, (GileadSciencesInc, Investigators Brochure Veklury (Remdesivir), 2020)

Day 1 IV	loading dose	5mg/kg (max 200mg) daily
Days 2-5	maintenance dose	2.5mg/kg (max 100mg) daily

Administration Lyophilized powder only – 100mg vial

Refer to the Childrens Medusa Monograph - Search "Remdesivir"

Extrapolated information for preparing doses for children under 3.5kg
(GileadSciencesInc, Personal Communication, 2020)

Loading Dose

Body weight (kg)	LOADING Dose (2.5mg/kg)	Total infusion Volume of 0.9% sodium chloride infusion bag	Volume withdrawn from infusion bag	Volume of reconstituted Remdesivir (100mg in 2ml)
1.5	3.75mg	12.5ml	0.75ml	0.75ml
2	5mg		1ml	1ml
2.5	6.25mg		1.25ml	1.25ml
3	7.5mg		1.5ml	1.5ml

Maintenance Dose

Body weight (kg)	MAINTENANCE Dose (1.25mg/kg)	Total infusion Volume of 0.9% sodium chloride infusion bag	Volume withdrawn from infusion bag	Volume of reconstituted Remdesivir (100mg in 2ml)
1.5	1.9mg	6.25ml	0.38ml	0.38ml
2	2.5mg		0.5ml	0.5ml
2.5	3.2mg		0.64ml	0.64ml
3	3.75mg		0.75ml	0.75ml

Stock must be transferred with the patient if moved ward

Monitoring

Daily completion by the medical team of the electronic Clinical Report Form recording patient response and progress – accessed via the initial emails sent to the Lead Physician

Viral infection assessment	twice weekly (every 2 days) SARS-COV-2 RNA clearance – **ETA or BAL** if intubated - or **NPA** if not intubated

	request for the **AUS COVID19 PCR** - write this on the request so it does not go for the Panther assay
Adverse drug reaction assessment (GileadSciencesInc, Investigators Brochure Veklury (Remdesivir), 2020)	hepatobiliary transaminases
Infusion related reactions (>0.01%)	hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. (Consider slower infusion rate) (GileadSciencesInc, Investigators Brochure Veklury (Remdesivir), 2020)

All drug or infusion reactions must be recorded on the Gilead eCRF and MHRA Yellow card scheme - https://yellowcard.mhra.gov.uk/yellowcards/reportmediator/

Interactions

In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and Pglycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1,OATP1B3, BSEP, MRP4, and NTCP.21 The clinical relevance of these in vitro assessments has not been established. (GileadSciencesInc, Investigators Brochure Veklury (Remdesivir), 2020)

(https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

Useful contact details

- Supply for an existing approved patient, please contact the Global team using the last email you received. This may have been from ClinOpsCOVID_SpecialPop@gilead.com; or RDV-CU-Reviewer@gilead.com

3. Education and Training

None

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Completion of Clinical Report Forms (CRF)	Submission to requestor within requested timescales	Head of Service	Per patient	Antimicrobial Working Party

5. Supporting References

Chiotos K, H. M. (2020, September 12). Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatric Infect Dis Soc.*, p. Published online.

GileadSciencesInc. (2020). *Investigators Brochure Veklury (Remdesivir)* (6 ed.). FosterCity: GileadSciencesInc.

GileadSciencesInc. (2020, November 19). Personal Communication.

Ltd, G. S. (2020). *Veklury 100 mg powder for concentrate for solution for infusion SmPC*. Retrieved November 19, 2020, from https://www.medicines.org.uk/emc/product/11597/smpc

NHSECommissioning. (2020). InterimCommissioningGuidance. London: NHSE.

6. Key Words

COVID 19, Pneumonia

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details			
Guideline Lead (Name and Title) David Harris Pharmacy UHL			**Executive Lead** Chief Medical Officer
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
19/11/20	1		New
24/11/20	2	S Bandi; S Bennett; B Saikai; M Zoha; C Ashton	
August 2021	3	D Harris	No changes
April 2022	4	D Harris	Severely immunocompromised and consent of parents/carer with efficacy & side effects info provided now included in eligibility criteria. Pharmacy contact details updated. Required patient information now includes current oxygen requirements.
November 2022	5	D Harris	Changes to commissioning policy for use in under 4 weeks/3kg