HSE Prescribing Protocol for Remdesivir use in the Treatment of COVID-19

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of patients with COVID-19 disease.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgement or specialist consultation.

INDICATION FOR USE: [1]

Refer to Summary of Product Characteristics (SmPC) of remdesivir for full prescribing information https://www.medicines.ie/medicines/veklury-100-mg-powder-for-concentrate-for-solution-for-infusion-34986/spc[1]

TREATMENT	INDICATION For the treatment of COVID-19 in:	ICD10	PROTOCOL CODE
Remdesivir (Veklury®)	1. Adults and paediatric patients (weighing at least 40kg) in **Tier 1/2** who: • Are less than or equal to 7 days of symptom onset • COVID-19 confirmed **within the last 5 days[2]** • do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	U07.1	COVID002
	2. Adult and paediatric patients (at least 4 weeks of age and weighing at least 3kg) hospitalised with pneumonia requiring supplemental oxygen (low or high flow oxygen or other non-invasive ventilation at the start of treatment)		

TREATMENT: [1]

Indication 1:	Day 1	Day 2	Day 3
Adults and paediatric (weighing at least 40kg) patients in **Tier 1/2** who : • Are less than or equal to 7 days of symptom onset • COVID-19 confirmed **within the last 5 days[2]** • do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	200mg loading dose	100mg once daily	100mg once daily

Indication 2:	Day 1	Days 2-5	Days 6-10
Adult and paediatric patients weighing at least 40kg hospitalised with pneumonia requiring supplemental oxygen (low or high flow oxygen or other non-invasive ventilation at the start of treatment)	200mg loading dose	100mg once daily	N/A
Paediatric patients at least 4 weeks of age and weighing at least 3kg but less than 40kg hospitalised with pneumonia requiring supplemental oxygen (low or high flow oxygen or other non-invasive ventilation at the start of treatment)	5mg/kg loading dose	2.5mg/kg	2.5mg/kg

ELIGIBLE PATIENTS:

- Patients meet all criteria outlined in the indication section

EXCLUSION CRITERIA:

- Patients who do not meet the eligibility criteria above

CONTRAINDICATIONS: [1]

- Hypersensitivity to the active substance or to any other ingredients

USE WITH CAUTION: [1]

- Women of child-bearing potential should be advised to use effective contraception during treatment and may require pregnancy test prior to initiating treatment.

- Transaminase elevations have been observed in clinical trials. Liver function should be determined in all patients prior to starting remdesivir and should be monitored while receiving it as clinically appropriate
  - Remdesivir should not be initiated in patients with alanine aminotransferase (ALT) greater than or equal to 5 x upper limit of normal (ULN) at baseline
  - Remdesivir should be discontinued in patients who, during treatment, develop[1]:
    i. ALT greater than or equal to 5 times the ULN. It may be restarted when ALT is less than 5 x ULN
    OR
    ii. ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)

OTHER INFORMATION:

- Multi-disciplinary team involvement should be sought prior to prescribing remdesivir for COVID-19. If available, advice should be sought from Infectious Disease, Microbiology colleagues or Respiratory and Critical Care Specialists[2].
- There is a limited amount of data from the use of remdesivir in pregnant women (less than 300 pregnancy outcomes). Most of the exposures occurred in the second, third or unknown trimester and available data do not indicate any risk. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures of the major metabolite of remdesivir that were around human therapeutic exposures. Due to very limited experience, remdesivir should not be used during first trimester in pregnancy unless the clinical condition of the woman requires treatment with it. Use in the second and third trimester of pregnancy may be considered[1].

METHOD OF ADMINISTRATION:

Refer to SmPC

DRUG INTERACTIONS:

Refer to SmPC

ATC CODE:

Antivirals for systemic use, direct acting antivirals, J05AB16

REIMBURSEMENT CATEGORY:

Hospital Reimbursement

REFERENCES:

1. Summary of Product Characteristics Veklury 100mg powder for concentrate for solution for infusion Available from: https://www.medicines.ie/medicines/veklury-100-mg-powder-for-concentrate-for-solution-for-infusion-34986/spc Accessed online: 04.10.2023
2. Expert opinion from The COVID-19 Therapeutic Advisory Group in July 2022
3. Royal College of Physicians of Ireland. National Immunisation Advisory Committee (NIAC). NIAC Immunisation Guidelines Chapter 05a: COVID-19. [Accessed on 01.12.2023]

Appendix 1: Clinical Prioritisation Framework for the Use and Prescribing of Remdesivir [2,3]

This guidance specifies which individuals might receive the greatest benefit from remdesivir. The treating physician will need to consider all co-morbidities and therapies to gauge for cumulative immune suppressing effect.

Tier	Risk Group
1	Immunocompromised adult patients not expected to mount an adequate immune* response to COVID-19 vaccination or SARS-coV-2 infection due to their underlying conditions, regardless of vaccine status (see appendix 2). Immunosuppressed adult patients taking rituximab within 12 months** and other B cell or T cell depleting therapies OR high dose steroids defined as adults receiving over 40mgs/day for more than 1 week or over 20mgs/day for two weeks within the last three months Children¥ with profound immunodeficiency (e.g. peri-transplant or CAR-T treatment) or who have specific congenital immune disorders (Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), Interferon pathway disorders) Unvaccinated adult patients at the highest risk of severe disease (adults aged over 70 years or adults aged over 50 years with **additional risks**)***
2	Unvaccinated adult patients at risk of severe disease not included in Tier 1 (adults aged over 50 years or adults aged under 50 years with **additional risks**)*** Unvaccinated children who are under hospital supervision for conditions such as severe complex neurodisability with multiple medical needs OR complex medical needs with multiple co-morbidities (e.g. technology dependent – tracheostomy, home ventilation etc)
3	Vaccinated adult patients at high risk of severe disease (adults aged over 70 years or adults aged over 50 years with **additional risks**)***
4	Vaccinated adult patients at risk of severe disease (adults aged over 50 years or adults aged under 50 with **additional risks**)***

*baseline or pre-treatment serology is not required

** Extended effect may occur and impact may be supported by consideration for serology testing

*** **Additional risks** include obesity (BMI over 35), diabetes mellitus, hypertension, cardiovascular disease, chronic lung disease, clinical risk factor conditions not meeting full definition for inclusion in Tier 1

¥Note that children have a significantly lower risk than adults of developing severe COVID-19, even when additional risks are present. Any decisions to treat are made in consultation with the paediatric ID team at CHI.

Appendix 2: Conditions or treatments associated with very high or high risk of severe COVID-19 disease[7]

May also include others, based on clinical judgement and a needs assessment.
Conditions in the shaded areas may be associated with a suboptimal response to vaccines.

Underlying Condition or Treatment	Very high risk	High risk
Cancer	Receiving or within 6 weeks of receiving systemic cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies Receiving treatment or pending treatment for a haematological cancer Undergoing or within 6 weeks of surgery or radical radiotherapy for lung or head and neck cancer Advanced/ metastatic cancer	Haematological[2] – within 5 years of treatment Non haematological cancer within 1 year following immunomodulating treatment* All other cancers being treated (excluding hormonal treatment)
Chronic heart and vascular disease		e.g., heart failure, hypertensive cardiac disease
Chronic Kidney Disease	On dialysis, or eGFR less than 15ml/min	eGFR less than 30ml/min
Chronic Liver Disease		e.g., cirrhosis or fibrosis
Chronic neurological disease or condition	With evolving respiratory failure requiring non-invasive ventilation e.g., motor neurone disease, spinal muscular atrophy	Significantly compromised respiratory function and/or the ability to clear secretions e.g, Parkinson's disease, cerebral palsy
Chronic respiratory disease	Severe e.g., severe cystic fibrosis, severe COPD, severe pulmonary fibrosis	Other conditions e.g., stable cystic fibrosis, severe asthma (continuous or repeated use of systemic corticosteroids), moderate COPD
Diabetes	HbA1c 58mmol/mol or greater	All other diabetes (Type 1 and 2)
Inherited metabolic diseases	Disorders of intermediary metabolism at risk of acute decompensation e.g., Maple Syrup Urine Disease	Disorders of intermediary metabolism not fulfilling criteria for very high risk

Underlying Condition or Treatment	Very high risk	High risk
Immunocompromise due to disease or treatment	Severe e.g., **Transplantation:** • Listed for solid organ or haematopoietic stem cell transplant (HSCT) • Post solid organ transplant at any time • Post HSCT within 12 months **Genetic diseases:** • APECED[3] • Inborn errors in the interferon pathway • Some B and T cell deficiencies **Treatment e.g.,** Cyclophosphamide, Rituximab, Alemtuzumab, Cladribine or Ocrelizumab in the previous 6 months	Other e.g., High dose systemic steroids[4] HIV, not on treatment or CD4 count less than 200 /10^6L for adults
Intellectual disability	Down Syndrome	Intellectual disability excluding Down Syndrome
Obesity	BMI greater than 40kg/m^2	BMI greater than 35kg/m^2
Severe mental illness		e.g., schizophrenia, bipolar disorder, severe depression
Sickle cell disease	Sickle cell disease	

[7]NIAC Immunisation Guidelines, Chapter 05a COVID-19 updated 29.11.2023

[2] Including e.g., leukaemia, lymphomas, blood dyscrasias or other malignant neoplasms affecting the bone marrow or lymphatic systems

*See Appendix 3 below – Therapies which may alter vaccine response

[3]APECED - autoimmune polyendocrinopathy candidiasis ectodermal dystrophy

[4]The following doses of prednisolone (or equivalent dose of another glucocorticoid) are likely to be immunosuppressive:

- Adults ≥10kg: ≥40mg/day for more than 1 week, or ≥20mg/day for 2 weeks or longer
- Children less than 10kg: 2mg/kg/day for 2 weeks or longer

Appendix 3: Therapies which may alter vaccine response

The following therapies are likely to interfere with vaccine responses, and patients may be considered in Tier 1
• Systemic calcineurin inhibitors (e.g. tacrolimus; ciclosporin) • Potent anti-proliferative agents (e.g Cyclophosphamide; Mycophenolate) • Some MS therapies (e.g Fingolimod and other S1P receptor modulators) • Abatacept (Orencia®) • Alemtuzumab (Lemtrada®) • Belimumab (Benlysta®) • Blinatumomab (Blincyto®) • Brentuximab vedotin (Adcetris®) • Daratumumab (Darzalex®) • Gemtuzumab ozogamicin (Mylotarg®) • Inotuzumab ozogamicin (Besponsa®) • Mogamulizumab (Poteligeo®) • Obintuzumab (Gazyvaro®) • Ocrelizumab (Ocrevus®) • Polatuzumab vodotin (Polivy®) • Rituximab (Blitzima®, Mabthera®, Ritemvia®, Rixathon®, Riximyo®, Truxima®)
The following therapies may interfere with vaccine effectiveness, or have relatively little data available. Patients receiving these therapies may fall into Tier 1. MDT discussion is recommended, possibly supported by antibody measurement if feasible.
• Some MS therapies (Timing of dosing in relation to vaccination may be relevant) • Azathioprine and 6-mercaptopurine (dependent on dose and duration) • Corticosteroids (depends on dose and duration, and relationship to vaccine doses.) • JAK inhibitors (varies with agent and underlying condition) • Anakinra (Kineret®) • Canakinumab (Ilaris®) • Risankizumab (Skyrizi®) • Sacituzumab govitecan (Trodelvy®) • Satalizumab (Enspryng®) • Tocilizumab (RoActemra®) • Tralokinumab (Adralza®)

The following therapies do not ordinarily impair vaccine responses and patients do not automatically fall into Tier 1 unless there is clinical or laboratory evidence of immunodeficiency, and a poor antibody response to SARS-CoV-2 vaccines.

- Topical calcineurin inhibitors
- Methotrexate
- DiMethylFumerate
- TNF alpha inhibitors
- IL-1 and IL-6 inhibitors
- IL-17/IL-23 inhibitors
- Adalimumab (and all approved biosimilars)
- Alirocumab (Praluent®)
- Atezolizumab (Tecentriq®)
- Avelumab (Bavencio®)
- Benralizumab (Fasenra®)
- Bevacizumab (Avastin®, Alymsys®, Zirabev®, MVASI®)
- Brodalumab (Kyntheum®)
- Brolucizumab (Beovu®)
- Burosumab (Crysvita®)
- Cemiplimab (Libtavo®)
- Certolizumab (Cimzia®)
- Cetuximab (Erbitux®)
- Denosumab (Prolia®, Xgeva®)
- Dupilumab (Dupixent®)
- Durvalumab (Imfinzi®)
- Eculizumab (Soliris®)
- Emicizumab (Hemlibra®)
- Enfortumab vodotin (Padcev®)
- Etanercept (Benepali®,Enbrel®, Erelzi®, Lifmior®)
- Erenumab (Aimovig®)
- Evolocumab (Repatha®)
- Golimumab (Simponi®)
- Guselkumab (Termfya®)
- Infliximab (Flixabi®, Inflectra®, Remicade®, Remsima®, Zessly®)
- Ipilimumab (Yervoy®)
- Ixekizumab (Taltz®)
- Lanadelumab (Takhzyro®)
- Mepolizumab (Nucala®)
- Natalizumab (Tysabri®)
- Nivolumab (Opdivo®)
- Omalizumab (Xolair®)
- Panitumab (Vectibix®)
- Pembrolizumab (Keytruda®)
- Pertuzumab (Perjeta®)
- Pertuzumab / Trastuzumab (Phesgo®)
- Ramucirumab (Cyramza®)
- Ranibizumab (Lucentis®, Byooviz®)
- Reslizumab (Cinqaero®)
- Romosozumab (Evenity®)
- Secukinumab (Cosentyx®)
- Tildrakizumab (Ilumetri®)
- Trastuzumab (Herceptin®)
- Trastuzumab deruxtecan (Enhertu®)
- Trastuzumab emtansine (Kadcyla®)
- Ustekinumab (Stelara®)
- Vedolizumab (Entyvio)

Expert opinion from The National Clinical Programme for Immunology Lead in July 2022