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DIRECTORATE GENERAL FOR COMMON NHS SERVICES PORTFOLIO AND PHARMACY

# PHARMACOCLINICAL PROTOCOL FOR THE USE OF REMDESIVIR (VEKLURY®) IN THE TREATMENT OF COVID-19 IN THE NATIONAL HEALTH SYSTEM

*Approved by the Permanent Pharmacy Commission*

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*All the experts have made a conflict of interest declaration*

# 1. INTRODUCTION

COVID-19 is caused by SARS-CoV-2, a coronavirus that was first identified in Wuhan, China in December 2019.

While most people with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease requiring oxygen therapy and 5% develop critical illness with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, thromboembolism and multi-organ failure, including acute kidney and heart damage[1].

There are several published studies that show the epidemiological data on the disease in Spain such as the Spanish SEMI-COVID-19 register[2] and the study carried out by the COVID-19@Spain Study Group[3].

On 3 July, the European Commission conditionally authorised Veklury (remdesivir) for the treatment of COVID-19 in adults and adolescents aged ≥ 12 years and weighing at least 40 kg with pneumonia requiring supplemental oxygen[4].

In Spain, remdesivir is not directly marketed and access is currently made through the Special Situations Medicines route, with restricted conditions of use. In addition, the current availability of the drug is very limited.
Remdesivir is a nucleotide analogue that exhibits in vitro activity against SARS-CoV-2, inhibiting its RNA replication. Currently, the available evidence on efficacy is limited and uncertain and some of the efficacy data from remdesivir clinical trials, e.g. virological assessment, will be provided post-authorisation.

So far, we have three published studies in which remdesivir is compared with placebo or with supportive care[5,6,7]. There is also another study comparing the use of remdesivir for 5 or 10 days[8] and a fifth, non-randomised study, showing the results of drug use in a group of 61 patients who entered a compassionate use programme[2].

ACTT-1[5] was the pivotal trial that resulted in conditional authorisation for remdesivir. The study followed an adaptive, phase III, double-blind, multicentre, randomised, placebo-controlled design to evaluate the efficacy and safety of remdesivir in hospitalised adults diagnosed with COVID-19. It included 1063 adult patients with PCR-confirmed SARS-CoV-2 infection and one of the following conditions: pulmonary infiltration and $SpO_2 \leq 94\%$ or the need for mechanical ventilation and/or supplemental oxygen. The primary endpoint was initially defined as time to clinical improvement within 15 days of randomisation. Clinical improvement was considered to be a reduction by at least two points on a 7-point ordinal scale, or hospital discharge, whichever occurred earlier. This primary endpoint was subsequently modified to be defined as time to recovery, where recovery is defined as the first day during the 28 days following randomisation in which the patient meets categories 1, 2 or 3 on the ordinal scale that finally resulted in eight categories, 1) not hospitalised with no activity limitation, 2) not hospitalised with activity limitation, requiring

home oxygen therapy, or both, 3) hospitalised with no need for oxygen therapy or continuing medical care (used if hospitalisation was extended for infection control reasons), 4) hospitalised not requiring oxygen therapy but requiring continuing medical attention, medical care or oxygen support, 5) hospitalised requiring oxygen therapy, 6) hospitalised with non-invasive mechanical ventilation or use of high-flow oxygen therapy, 7) hospitalised with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) and 8) death. This change in variable was justified by the emergence of new information that COVID-19 might have a longer course. The ordinal scale previously consisted of 7 categories and later became 8 by splitting category 3 into two different categories. These changes may affect the outcomes of the primary endpoint.

The most important secondary endpoints were mortality at 14 and 28 days and comparison of the subjects' clinical status at day 15. This comparison was made based on the ordinal scale with 8 categories.

The patients in the remdesivir group had a shorter recovery time than patients in the placebo group (median, 11 vs. 15 days; recovery rate index, 1.32; 95% confidence interval (CI), 1.12 to 1.55; P < 0.001; 1059 patients). Among patients with an initial ordinal category of 5, corresponding to inpatients requiring supplemental oxygen (without the need for high-flow oxygen devices) (421 patients), the recovery rate was 1.47 (95% CI, 1.17 to 1.84); among patients with a baseline category 4 (127 patients) and those with a baseline category 6 (197 patients), the estimated rate ratios for recovery were 1.38 (95% CI, 0.94 to 2.03) and 1.20 (95% CI, 0.79 to 1.81), respectively. For those receiving mechanical ventilation or ECMO at enrolment (baseline ordinal scores of 7; 272 patients), the recovery rate ratio was 0.95 (95% CI, 0.64 to 1.42).

Preliminary results from this trial suggest that a 10-day course of remdesivir shortens clinical recovery compared to placebo by four days.

However, for mortality, a secondary endpoint, the difference was not significant compared to the placebo group (hazard ratio (HR) 0.70, 95% CI 0.47 to 1.04) at 14 days of treatment. The 28-day mortality data are not yet available.

The benefit was most evident in patients with a baseline ordinal score of 5 (requiring oxygen), a finding that is probably due to the larger sample size in this category (as the test on treatment interaction by baseline ordinal score was not significant).

Wang et al.[6] conducted a double-blind, multicentre, placebo-controlled phase III study that included 237 patients with severe COVID. This study showed no reduction in clinical deterioration (HR 1.23 [0.87-1.75]). In the case of 28-day mortality (secondary endpoint) there was no significant difference compared to placebo (14% *vs* 13%, difference 1.1%; 95% CI [-8.1% to 10.3%]). This study was terminated prematurely before reaching the planned sample size the investigators (453 patients) had calculated would be needed to demonstrate differences with adequate statistical power.

In another randomised phase III open-label trial, which aimed to compare two durations of treatment with remdesivir (5 and 10 days) in severe COVID-19 patients, the median length of hospitalisation at day 14 in the 5-day treatment group was 10 days versus 11 days in the 10-day treatment group. Mortality was 8% in the 5-day regimen and the 10.7% for the 10-day regimen[8]. This trial showed no significant difference between the 5-day and 10-day regimen in terms of clinical benefit and is the basis for a standard recommendation of a 5-day regimen of remdesivir.

On the other hand, Spinner et al[7] conducted a trial in patients with moderate COVID-19 ($SpO_2$ >94%); the patients assigned to remdesivir treatment for 10 days showed no statistically significant difference with standard care in clinical status at 11 days of treatment. For the patients treated for 5 days with remdesivir, although they had a statistically significant difference in clinical status versus standard care, the clinical significance of this was uncertain.

It should be noted that in the two studies that evaluated the 10-day regimen, 38% of patients completed it in the study by Spinner et al.[7] and 44% of the patients in Goldman et al.[8]

With the limited evidence available, it seems that the patients with the best results are hospitalised patients who require low-flow oxygen therapy. Current data show no benefit in patients who have progressed in their disease to requiring high-flow oxygen therapy or non-invasive or invasive mechanical ventilation or ECMO. For these patients the options should be limited to inclusion in clinical trials.

Therefore, based on currently available evidence, we have no data showing remdesivir has a beneficial effect on mortality compared to placebo or supportive care. In addition, the results for the 5-day treatment appear more favourable than those from the 10-day treatment and this may represent a pathophysiological inconsistency. It should also be noted that there are possible heterogeneities in the response between subgroups and that there is still no less uncertainty about the efficacy of the treatment. These facts should be considered in establishing both the selection and monitoring criteria for treatment, as well as in establishing the added value of the medicine and the need for outcome and effectiveness monitoring in actual practice.

In children below 12 years of age, who are not included in the therapeutic indication of the authorised SMPC, there are no data from clinical trials, and limited data are available on the use of remdesivir.

Access to the medicine during pregnancy and for children under 18 years of age who do not meet the criteria defined in this pharmacoclinical protocol is through a specific compassionate use programme and is not the subject of this pharmacoclinical protocol. For patients < 18 years of age with compassionate use access, a specific clinical follow-up will be designed through VALTERMED.

## 2. TREATMENT OBJECTIVE

The objective of antiviral treatment with remdesivir is to prevent the progression of disease severity, to promote the clinical recovery of patients and, thus, to indirectly reduce the length of hospital stay for patients with COVID-19.

Furthermore, the need has been established to measure the efficiency of the use of remdesivir in decongesting the healthcare system (see section 3) by reducing the consumption of healthcare resources derived from the hospitalisation of eligible patients, shortening the length of their hospital stay and therefore increasing the healthcare capacity of the Health System.

## 3. PATIENT SELECTION CRITERIA

**Hospitalised patients with severe COVID-19 pneumonia** who meet all of the following criteria are considered candidates for treatment with remdesivir:

- Adults and adolescents aged ≥12 years and weighing ≥ 40 Kg
- Patients requiring supplemental oxygen that is reversed with low-flow oxygen therapy (nasal cannula or simple mask, with or without reservoir).
- Patients with PCR-confirmed SARS-CoV-2 infection who have had symptoms for up to 7 days.
- Patients with the disease exhibiting at least two of the following three criteria:
    - Respiratory rate ≥ 24 rpm
    - $SpO_2$ <94% on room air
    - Arterial partial pressure of oxygen / fraction of inspired oxygen (PaO2/FiO2) ratio < 300 mmHg

**Remdesivir should not be administered in the following cases:**

- Patients with severe disease who require non-invasive ventilation or use of high-flow oxygen devices, invasive mechanical ventilation or ECMO
- Severe liver disease: ALT or AST ≥ 5 times the upper limit of normal (ULN)
- Patients with severe renal impairment (glomerular filtration rate < 30 ml/min), on haemodialysis, peritoneal dialysis.
- Those requiring two ionotropics to maintain blood pressure
- Pregnant women, breast-fed infant or who have tested positive for pregnancy[a]
- Evidence of multiple organ failure.

[a] There are no or limited data on the use of remdesivir in pregnant women. Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it. Access to the drug during pregnancy is, at the time of approval of this protocol, through a specific compassionate use programme. Women of childbearing age should use effective contraception during treatment. It is not known whether remdesivir is excreted in human milk or the effects on the infant or on milk production.

**Criteria for discontinuation of remdesivir**

- Worsening liver function:
  - ALT / AST ≥ 5 times ULN
  - A 3-fold elevation in ALT above ULN and 2-fold elevation in conjugated bilirubin above ULN.
- Worsening renal function: glomerular filtration rate (ml/min) < 30 ml/min

## 4. GENERAL CONSIDERATIONS FOR TREATMENT WITH REMDESIVIR

In accordance with the summary of product characteristics[11], the recommended treatment is as follows:

Loading dose on day 1: 200 mg IV

Subsequent daily doses: 100 mg/day IV

*Duration of the treatment in the current context:*

It is recommended not to exceed 5 days of treatment with a maximum of 6 vials[8].

In relation to special populations, patients older than 65 years of age do not require dose adjustment. The pharmacokinetics of the drug have not been evaluated in patients with renal or hepatic impairment. Patients with GFR ≥ 30 ml/min have received treatment without dose adjustment, but it should not be used in those with GFR < 30 ml/min.

The recommendations included in the summary of product characteristics[11] regarding special warnings and precautions for use should be taken into account.

*Risk of decreased antiviral activity when co-administered with other medicines*

Concomitant administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate[b] is not recommended based on *in vitro* data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir. According to the RECOVERY study[12], the use of hydroxychloroquine was associated with an increased length of hospital stay and an increased risk of progression to severe conditions or death. The SOLIDARITY trial[13] also failed to demonstrate a reduction in mortality in patients treated with either hydroxychloroquine or lopinavir/ritonavir[b], antiviral combinations also considered for the treatment of COVID-19.

Co-administration with rifampicin, carbamazepine, phenobarbital, phenytoin, primidone and Hypericum is also not recommended[15].

[b] Currently, these treatments are not indicated for the treatment of COVID-19 given their negative results in clinical trials.

## 5. EVALUATION AND MONITORING

The physician responsible for the patient in each of the stages of the process must record the following information in VALTERMED.

**General patient details (to be collected in VALTERMED before starting treatment to carry out the evaluation):**

- NHS Code[c]
- CIP/CITE code[c]
- NIF/NIE[c]
- Health Card No.[c]
- NHC
- Sex[d]
- Date of birth[d]

**Disease characterisation at the beginning of treatment**

- Date of start of symptoms:
- Date of hospitalisation:
- Meets selection criteria for patients with severe COVID-19 pneumonia requiring supplemental oxygen that is reversed with low-flow oxygen therapy: Date:
    - Respiratory rate > 24 rpm: yes/no
    - Baseline SpO2 < 94%: yes/no
    - Arterial oxygen partial pressure / inspired oxygen fraction (PaO2/FiO2) ratio < 300 mmHg: yes/no
- Date of analysis:
- Baseline ALT (U/l) ≤ 5 times ULN: yes/no
- Baseline AST (U/L) ≤ 5 times ULN: yes/no
- Baseline glomerular filtration rate (ml/min) ≥ 30 ml/min: yes/no

**Analytical data at the beginning of treatment (optional):**

- Date of analysis:
- C-reactive protein (mg/l):
- Ferritin (mcg/l):
- LDH (U/L):

[c] It is mandatory to fill in at least one of these fields.
[d] Mandatory fields.

- D-Dimer (ng/ml):
- Baseline lymphocyte count (x$10^6$/l):

**Concomitant treatments for COVID-19 during admission**: (optional)

- Corticosteroids: yes/no
- Other:

**REMDESIVIR administration (mandatory):**

- Date of first dose:
- Number of vials used:_____vials:
- Premature discontinuation of treatment (Complete treatment without premature discontinuation / premature discontinuation due to serious side effects* / intolerance / liver disorders / worsening / death/ supply shortage)

  * In case of adverse effects, complete description in the corresponding section below

**Final clinical evaluation of the disease (mandatory):**

- Hospital discharge confirmed: if yes, time in days spent in hospital (from day 1 of initiation of treatment):
- Hospital discharge date (discharge from Covid-19 treatment):
- Death confirmed: yes/no if yes, date of death:

**Final clinical status (mandatory):**

- Worsening of clinical status: yes/no if yes,
  - ICU admission: yes/no date of admission: Duration ICU admission:
  - Need for high flow oxygen devices: yes/no Start date: Duration:
  - Need for non-invasive ventilation: yes/no Start date: Duration:
  - Need for ECMO: yes/no Start date: Duration:
  - Need for invasive mechanical ventilation: yes/no Start date: Duration:
- Baseline ALT (U/l)≤ 5 times ULN: yes/no
- Baseline AST (U/L) ≤ 5 times ULN: yes/no
- Glomerular filtrate (ml/min) ≥ 30 ml/min: yes/no
- Conjugated bilirubin (mg/dl) >2 times ULN: yes/no

**Final analytical data (optional):**

- Date of last analysis:
- C-reactive protein (mg/l):
- Ferritin (mcg/l):
- LDH (U/L):
- D-Dimer (ng/ml):
- Baseline lymphocyte count ($x10^6$/l):

**Safety** (optional)

- Hypotension: yes/no
- Nosocomial respiratory infection: yes/no
- Renal failure: yes/no
- Cardiac arrest: yes/no
- Septic shock: yes/no
- Atrial fibrillation: yes/no
- Respiratory distress syndrome:
- Thromboembolic or ischemic complications: yes/no
- Pneumothorax: yes/no
- Severe liver disorders: yes/no
- Any other adverse effect:

Under no circumstances should any data collection compete with the legal obligations under which all suspected adverse reactions will be reported through your pharmacovigilance centre (www.notificaram.es).

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