Remdesivir in the therapy of adult patients with COVID-19

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Useful elements are provided below to guide the prescription and to define a relationship between the benefits and risks of the medicine for the individual patient.	
For which patients is it recommended?	***Subjects not hospitalised for COVID-19*** Treatment of Coronavirus disease 2019 (COVID-19), in adults not hospitalised for COVID-19 and not on oxygen therapy for COVID-19 with onset of symptoms for no more than 7 days and in the presence of predisposing clinical conditions that represent risk factors for developing severe COVID-19. The patient must not be hospitalised for COVID-19 and should show at least one of the following risk factors associated with development to severe disease: • Oncological/oncohematological pathology in the active phase • Chronic renal failure (excluding patients on dialysis or with an eGFR<30 mL/min/1.73 m^2) • Severe pulmonary disease • Primary or acquired immunodeficiency • Obesity [(Body Mass Index, BMI) ≥30] • Severe cardiovascular disease (heart failure, coronary artery disease, cardiomyopathy) • Uncompensated diabetes mellitus ***Subjects hospitalised for COVID-19*** From the beginning, through the monitoring registry, AIFA has granted **reimbursement for remdesivir exclusively for subjects with COVID-19 pneumonia on oxygen therapy who do not require high flow oxygen or mechanical ventilation or ECMO and with onset of symptoms for less than 10 days**. AIFA establishes, in the light of the new available evidence, that the use of remdesivir in the population admitted to reimbursement **can be considered only in selected cases, after a careful assessment of the benefit/risk ratio**. The data currently available on remdesivir, in fact, are not consistent and overall do not demonstrate a clear clinical benefit in terms of mortality or use of mechanical ventilation. The WHO, after conducting a randomised trial and a meta-analysis of the efficacy trials in over 7,000 patients, has made a **WEAK NEGATIVE recommendation** on the use of this medicine in the entire population of patients with COVID-19 regardless of severity. Although a reduction in time to recovery and mortality was demonstrated in the subgroup of subjects on standard (low flow) oxygen therapy in the pivotal study ACTT-1, this was not confirmed by the Solidarity study and the meta-analysis of the four available studies. Furthermore, according to the WHO, the results by subgroups cannot be considered reliable for accurate estimates.

	All studies agree on the lack of efficacy in the most severe patients (who require oxygen delivery through high-flow devices, mechanical ventilation – non-invasive/invasive – or ECMO). The main risks associated with the use of the medicine are represented by possible liver and kidney toxicity (the latter is currently being investigated by the EMA). Finally, in compliance with what is reported in the technical data sheet, the medicine is not recommended in patients with severely impaired renal function (eGFR<30mL/min) and should not be used in patients with ALT ≥ 5 times the nomral upper limit at baseline (section 4.4 SmPC). Please note that the medicine is not authorised before 12 years of age.
At what dosages is it preferably prescribed and in what forms?	***Recommended dosage*** The recommended dosage of remdesivir in adults and adolescents (aged 12 to less than 18 years weighing at least 40 kg) is: • day 1: single loading dose of remdesivir 200 mg administered by intravenous infusion • from day 2 onwards: 100 mg administered once a day by intravenous infusion. ***Duration of treatment*** ***Subjects not hospitalised for COVID-19*** Treatment should be started as soon as possible after the diagnosis of COVID-19 and within 7 days of the onset of symptoms. The total duration of treatment should be 3 days. Patients should be monitored during treatment with remdesivir. Administration of the drug in an outpatient setting should be monitored according to local practice. Use should be in settings where it is possible to treat severe hypersensitivity reactions, including anaphylaxis. ***Subjects not hospitalised for COVID-19*** The total duration of treatment should be at least 5 days and must not exceed 10 days. Studies conducted so far have not shown a difference in efficacy between the 5-day treatment and the 10-day treatment, either in patients with moderate disease or in the severe disease cohort. For special situations, please refer to the technical data sheet of the Veklury® medicine.
Who can prescribe the medicine in this emergency phase?	The Veklury® medicine has been made available by the European Commission through a European Joint Procurement procedure and is subject to the AIFA monitoring registry (https://www.aifa.gov.it/-/attività-registro-veklury-remdesivir-) Remdesivir is a hospital medicine that can be prescribed by the infectious disease specialist, pulmonologist, or other clinician operating in the centres for managing COVID-19 indicated by the Region.
What are the major risks in terms of adverse reactions?	**Warnings** (from data sheet)**:** • Increased transaminases • Renal impairment For more safety information please refer to the recently published data sheet and studies. https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_it.pdf.

Can it be prescribed together with other medicines?	**Main Interactions** (from data sheet)**:** No interaction studies with remdesivir have been performed. The overall interaction potential is currently unknown; therefore, patients should remain under close observation when they are administered remdesivir. Due to the antagonism observed in vitro, the concomitant use of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended. In any case, please note that the use of the latter medicines outside clinical trials is not authorised. The use of strong CYP450 enzyme inducers (for example rifampicin) is not recommended as they can reduce the plasma concentrations of remdesivir. No data are available regarding co-administration with dexamethasone (CYP3A4 substrate). For more information on drug interactions, see the technical data sheet and consult the website: https://www.covid19-druginteractions.org/.

Background

Remdesivir (Veklury®, 100 mg concentrate for solution for infusion) is the first antiviral medicine to be authorised by the European Medicines Agency (EMA) with specific indication for the "treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and over and weighing at least 40 kg) with pneumonia requiring supplemental oxygen therapy". In December 2021, the EMA authorized an extension of indication relating to the treatment of coronavirus disease 2019 (COVID-19) in "adults who do not require supplemental oxygen therapy and have an increased risk of progression to severe COVID-19".
Veklury has been authorised in Europe under a 'conditional' procedure, which means that further data on this medicine should be provided. The EMA will review the new data at least annually, updating, if necessary, the summary of product characteristics (SmPC).

Rationale

Remdesivir is a nucleotide analogue prodrug of adenosine that is metabolised in host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analogue of adenosine triphosphate (ATP) and competes with the natural substrate of ATP for incorporation into nascent RNA chains by SARS-CoV-2 RNA-dependent RNA polymerase, causing termination of the delayed chain during viral RNA replication.
Remdesivir showed in vitro activity against a clinical isolate of SARS-CoV-2 in primary cells of the human respiratory epithelium.

Main evidence available

Randomised clinical studies

Data from 4 randomised controlled studies that studied remdesivir in different contexts are currently available:

- *29/04/2020 - Wang J et al. 2020 (NCT04257656)*: This is a randomised double-blind vs placebo controlled study that was conducted in the period between 6 February 2020 and 12 March 2020, at 10 hospital centres in the province of Hubei, China. The study enrolled adult hospitalised subjects, with onset of symptoms within a maximum of 12 days of enrolment, with radiologically confirmed pneumonia and O_2 saturation≤94% in ambient air or P/FiO2 ratio≤300mmHg. Both groups were taking combined therapies

(18.5% interferon alfa 2b, 18% lopinavir/ritonavir, 79% antibiotics and 39% corticosteroids). Enrolled subjects were randomised in a 2:1 ratio to take remdesivir (200 mg iv on day 1 and 100 mg from day 2 for up to a total of 10 days of treatment) or placebo. The primary endpoint of the study was time to clinical improvement at day 28, defined as the time (in days) from randomisation to the time when there was a two-level reduction on a six-point ordinal scale in clinical status (from 1 = discharged to 6 = death) or discharge from hospital. The study enrolled 237 patients (158 randomised to the remdesivir group and 79 to the placebo group). The use of remdesivir was not associated with a difference in time to clinical improvement (RR 1.23 [95% CI 0.87-1.75]). In the subgroup of patients with symptom duration of no more than 10 days, there was a trend in the remdesivir arm for more rapid clinical improvement at the limits of statistical significance (RR 1.52 [0.95–2.43]) compared to subjects who received placebo. No significant differences were found in terms of mortality at 28 days. In the population studied, consisting predominantly of subjects with severe COVID-19 disease, who largely required oxygen therapy at hospitalisation, remdesivir did not improve clinical outcomes and did not statistically significantly reduce mortality. In interpreting the results, however, it should be taken into account that, due to the epidemiological trend of the disease in China with the reduction in cases following social distancing policies, the study was interrupted early due to difficulties in patient recruitment and the sample was therefore reduced compared to initial forecasts. The study was therefore not dimensioned for the evaluation of study outcomes and the results obtained do not allow defining the benefit/risk profile of the medicine.

Main critical issues:

- the study failed to reach the estimated sample size.

- *22/05/2020 - Beigel JH et al. 2020 (ACTT-1 Trial; NCT04280705)*: This is a large, double-blind, multinational randomised clinical trial sponsored by the National Health Institutes in the USA that evaluated the efficacy of remdesivir vs placebo (both administered for 10 days) in a population that included hospitalised subjects, largely in need of oxygen therapy. The published results refer to a preliminary analysis carried out when the expected sample was reached but not all enrolled subjects had completed the 28-day follow-up. The main inclusion criteria were as follows: adult patients hospitalised with radiologically demonstrated pneumonia, or with O_2 saturation $\leq$94% in ambient air or need for supplementation with oxygen mechanical ventilation or ECMO (extracorporeal oxygenation). The primary outcome was the time to recovery (discharge or hospitalisation without the need for additional care), while the secondary outcome was mortality at 14 days. The study enrolled 1063 subjects, while the published results referred in total to 1059 subjects (538 in the remdesivir group and 521 in the placebo group). In total, 88.7% of the study population had severe disease, specifically 25.6% received mechanical ventilation or ECMO, 18.5% received non-invasive ventilation or high-flow oxygen, 39.6% received supplemental oxygen, and the remaining 11.9%, despite receiving hospital care, did not need oxygen; 52% had 2 or more associated pathologies, 29% had diabetes. Median time to symptom onset was 9 days. Combination therapy has not been described. The data obtained showed a statistically significant superiority of remdesivir over placebo in the general population of hospitalised patients with COVID-19, with a 4-day difference in recovery time in patients in the remdesivir group compared to those in the placebo group (11 vs 15 days HR: 1.32, 95% CI 1.12 - 1.55; p <0.001). In the population stratum with pneumonia and need for supplemental oxygen, the difference in median recovery time was 12 days in the remdesivir group versus 18 in the placebo group (RR 1.36; 95% CI 1.143-1.623; p <0.001). No difference was observed in the population stratum with 'mild-moderate' disease (stage 4; RR 1.38; 0.94-2.03). Compared to placebo, no differences emerged in patients hospitalised on ventilatory support (non-invasive ventilation and high-flow devices; RR 1.20; 95% CI 0.79-1.81) and on mechanical ventilation (invasive mechanical ventilation and ECMO; RR0.95; 95% CI 0.64-1.42). In the general population receiving remdesivir, a more favourable trend in terms of mortality was observed at 14 than in the

placebo group without reaching statistical significance; HR 0.70; 95% CI 0.47-1.04), but the study was not sized for the evaluation of the latter outcome, even considering its early termination.

Main critical issues

- Early interruption
- The study was not sized to evaluate a reduction in mortality
- Associated therapies have not been described

- *27/05/2020 - Goldman JD et al. 2020 (GS-US-540-5773 Trial; NCT04292899)*: This is a randomised, open-label study sponsored by the company Gilead, in which the efficacy of remdesivir administered for 5 or 10 days was evaluated in subjects with severe COVID-19 disease, defined by the presence of interstitial pneumonia with $SaO_2 \leq 94\%$ in ambient air. The study was conducted from 6 to 26 March in 55 centres in the US, Europe and Asia. The primary endpoint was the clinical stage on day 14 on an ordinal scale of 7 points ranging from death (score = 1) to discharge (score = 7). A total of 397 subjects were randomised 1:1 to receive remdesivir for 5 days (n = 200) or remdesivir for 10 days (n = 197). At baseline, patients randomised to the 10-day treatment group had significantly worse clinical status than those randomised to the 5-day group (P = 0.02). The median treatment time was 5 days (IQR 5-5) for the group randomised to the remdesivir arm (with 76% of subjects ending treatment) and 9 days (IQR 6-10) in the group randomised to remdesivir-10 days with only 44% of subjects completing treatment for the entire duration. Median time to symptom onset was 8.5 days. Any combination therapies have not been described. At day 14, clinical improvement of 2 or more points on the ordinal scale occurred in 64% of patients in the 5-day treatment group and 54% in the 10-day group. After statistical adjustment for baseline clinical status, patients treated for 10 days had a distribution in clinical status on day 14 comparable to that of the 5-day group (P = 0.14). A similar absence of difference was found with regard to the secondary efficacy endpoints, in particular in the 5-day group there was a numerically lower mortality rate compared to the 10-day group (8% vs 11%), although not statistically significant.

  Main critical issues

  - open-label design
  - absence of a control arm
  - lack of stratification by baseline disease severity with consequent important imbalance of the study population
  - use of an endpoint of uncertain clinical relevance
  - attrition bias particularly in the active treatment arm at 10 days.
- *21/08/2020 - Spinner CD et al. 2020 (GS-US-540-5774 Trial; NCT04292730)*: This is a randomised, open-label, placebo-sponsored study by Gilead, evaluating the efficacy of remdesivir (administered for 5 or 10 days) versus standard-of-care in subjects with moderate COVID-19 disease, defined by the presence of interstitial pneumonia with $SaO_2 > 94\%$ in ambient air. The study was conducted between 15 March and 18 April 2020 in 105 centres in the US, Europe and Asia. A total of 596 subjects were randomised in ratio 1:1:1 to receive remdesivir for 10 days (n = 197), remdesivir for 5 days (n = 199), or standard-of-care (n = 200). The primary endpoint was the clinical stage on day 11 on an ordinal scale of 7 points ranging from death (score = 1) to discharge (score = 7). Patients assigned to the 3 groups were balanced for demographics and comorbidities. Overall, 56% of patients had cardiovascular disease, 42% hypertension, 40% diabetes and 14% asthma. The median treatment time was 5 days for the remdesivir-5-day randomised group (with 76% of subjects ending treatment) and 6 days in the remdesivir-10-day randomised group with only 38% of subjects completing the treatment until the 10th day. Median time to symptom onset was approximately 8 days. The three groups took combination therapies (hydroxychloroquine, lopinavir ritonavir, azithromycin in an unbalanced way in favour of the standard of care group, and 17% corticosteroids in a balanced way). At day 11, patients receiving remdesivir for 5 days had a significantly higher probability of a better distribution of clinical status on the 7-point ordinal

scale than those randomised to treatment with standard therapy (OR 1.65; 95% CI 1.09 -2.48; P = 0.02). On the contrary, between the 10-day remdesivir treatment group and the standard treatment group, the difference in the distribution of clinical status at day 11 was not statistically significant (P = 0.18). There were no significant differences between the active and standard therapy arms in terms of exploratory efficacy endpoints, including time to clinical improvement, length of hospitalisation and mortality.
Main critical issues

- open-label design
- use of an endpoint, represented by the distribution on an ordinal scale, difficult to interpret in terms of clinical relevance of the results (McCreary EK, Angus DC. 2020)
- attrition bias particularly in the active treatment arm at 10 days
- lack of a formal comparison between the two treatment durations.

- *08/10/2020 Beigel JH et al. 2020 (ACTT-1 Trial; NCT04280705.)*: The data are published of the final analysis of the ACTT-1 study referring to a total of 1062 randomised subjects (541 assigned to remdesivir and 521 to the placebo group). In total, 90.1% of the study population showed a severe disease, specifically 26.8% received mechanical ventilation or ECMO, 18.2% received non-invasive ventilation or high-flow oxygen, 41.0% received supplemental oxygen, and the remaining 13%, while receiving hospital care, did not require oxygen. Regarding the comorbidities, 50.7% were hypertensive, 45.4% were obese and 30.6% had diabetes. During the study, 373 patients (35.6%) received hydroxychloroquine and 241 (23.0%) received a glucocorticoid. Time to clinical recovery (primary outcome) was 10 days (median, 95% CI 9-11), compared with 15 days (95% CI 13-8) among those who received placebo (RR 1.29; CI 95% 1.12-1.49; P <0.001). Mortality estimates in remdesivir-treated subjects versus placebo were 6.7% vs 11.9% at 15 days and 11.4% vs 15.2% at 29 days, respectively (HR 0.73; 95% CI 0.52-1.03). By stratifying the population by baseline disease severity, the clinical benefit, both in terms of time to recovery and mortality, was recorded only for subjects on standard oxygen therapy, while no clinical benefit was observed in subjects on high flow oxygen therapy or mechanical ventilation or ECMO.
- *15/10/2020 SOLIDARITY Trial (Pan H et al. 2020)*: the results of the SOLIDARITY study, an adaptive, multicentre study, coordinated by the WHO, aimed at testing the efficacy and safety of different anti-COVID strategies, were disclosed (including, originally, HCQ, remdesivir, lopinavir/ritonavir and interferon). Eligible subjects were of legal age, hospitalised with a diagnosis of COVID-19, naïve for the medicines under study. In the period between March and April, over 11,330 were randomised by 405 hospitals in 30 different countries in the 6 continents. The main analysis was performed on 11,266 participants, of which 2,750 assigned to the remdesivir arm (for a duration of 10 days of treatment). In the primary analysis relating to mortality, the use of remdesivir was not associated with any benefit [RR = 0.95; 95% CI 0.81-1.11, P = 0.50; 301/2743 vs 303/2708)]. Subjects undergoing mechanical ventilation (both non-invasive and invasive) had a tendency, albeit not statistically significant, to a worse clinical outcome (RR = 1.26; 95% CI 0.65-2.46). To estimate the effect of the medicine on mortality, the authors also conducted a meta-analysis of 4 studies in which remdesivir was used [SOLIDARITY (604 deaths out of about 5000 randomised), ACTT-1 (136 deaths out of about 1000) and two smaller studies (41 deaths)]. Data analysis confirmed the absence of clinical benefits of remdesivir in terms of mortality reduction (RR = 0.91; 95% CI 0.79-1.05) in the general population. Analysing the data in the low-risk population (in the absence of ventilation), a trend towards the limits of statistical significance (RR = 0.80; 95% CI 0.60-1.01) was observed, while a trend towards a worse outcome was confirmed in subjects at other risk. (RR = 1.16; 95% CI 0.85-1.60).
- *14/09/2021 DisCoVeRy Trial (Ader F et al. 2021)*: DisCoVeRy is a phase 3, open-label, adaptive, multicentre, randomized and controlled platform trial conducted in 48 centers in Europe (France, Belgium, Austria, Portugal, Luxembourg). Adult hospitalized subjects were eligible with laboratory confirmed SARS-CoV-2 infection and disease of any duration with clinical evidence of hypoxemic

pneumonia or requiring oxygen supplementation. Participants were randomized (1: 1: 1: 1: 1) to receive standard of care (SOC) or remdesivir, lopinavir-ritonavir, lopinavir – ritonavir, and interferon beta-1a or hydroxychloroquine. Remdesivir was administered as an intravenous infusion of 200 mg on day 1, followed by 1h once daily infusions of 100 mg for up to 9 days, for a total duration of 10 days. The primary endpoint was the clinical status at day 15 measured by the WHO seven-point ordinal scale. Between 22 March 2020 and 21 January 2021, 857 participants were enrolled and randomized to remdesivir plus standard of care (n = 429) or standard of care only (n = 428). The median age at enrollment was 64 years and 7% of the participants had at least one co-morbidity. 40% of subjects had severe COVID-19, 18% of subjects were on oxygen supplementation with high-flow devices, and 17% were on invasive mechanical ventilation. 40% of subjects were taking corticosteroids at the same time and 52% were taking anticoagulants. At day 15, the WHO ordinal scale distribution was not statistically different in the remdesivir group compared to the SOC group (OR 0.98; 95% CI 0.77-1.25; p = 0.85). In addition, 2,852 nasopharyngeal swabs from 677 participants were analyzed: the mean reduction in viral loads between baseline and day 3 was similar in the remdesivir group and the control group.

Main critical issues:

- open-label design
- viral kinetic data available only in subgroup of subjects.

- *22/12/2021 PINETREE Trial (Gottlieb RL et al. 2021)*: This is a randomized, double-blind, placebo-controlled study that enrolled non-hospitalized subjects with a confirmed diagnosis of COVID-19 with onset of symptoms within the previous 7 days and who had at least one risk factor for progression to severe COVID-19 (age ≥60 years, obesity or coexisting medical conditions). Patients were randomized to receive intravenous remdesivir (200 mg on day 1 and 100 mg on day 2 and 3) or placebo. The primary efficacy endpoint was a composite endpoint of hospitalization for COVID-19 or death from any cause by day 28. The study was terminated early for reasons external to the conduct of the study, mainly related to the decrease in the incidence of SARS-CoV-2 infections, to ethical concerns regarding the assignment of patients to placebo in the context of greater access to authorized treatments for emergency use such as monoclonal antibodies and increased vaccination rates among high-risk people. Of the 1264 patients who should have enrolled, a total of 562 patients were randomized and included in the analyses: 279 patients in the remdesivir group and 283 in the placebo group. The mean age was 50 years, 47.9% of the patients were women. 30.2% of patients were> 60 years of age and the most common coexisting conditions were diabetes mellitus (61.6%), obesity (55.2%) and hypertension (47.7%). The mean duration of symptoms prior to initiation of treatment was 5 days (IQR, 3-6), and the median time from SARS-CoV-2 confirmation to screening was 2 days (IQR, 1- 4). The primary endpoint occurred in 2 subjects (0.7%) in the remdesivir group and 15 (5.3%) in the placebo group (RR 0.13; 95% CI 0.03-0.59; P = 0.008). A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a COVID-19-related physician visit on day 28 (RR 0.19; CI 95 % 0.07-0.56). No deaths were recorded by day 28.

  Main critical issues:

  - inaccuracy bias due to early study termination (less than half of the patients were enrolled compared to the planned sample size).

Scientific reviews and meta-analyses - Subjects hospitalised for COVID-19

Scientific reviews and meta-analyses updated in real time ("living systematic review and network meta-analysis") conducted by international organisations or major research groups summarising the results of clinical trials available from time to time have become available. With regard to the use of remdesivir in hospitalised subjects, please note that:

- In the meta-analysis accompanying the living guideline on remdesivir (updated on 20/11/2020), WHO examines 7,333 subjects treated in the 4 main clinical studies that evaluated the efficacy of remdesivir (ACTT-1; SOLIDARITY; SIMPLE-MODERATE, and Wang et al.). The analysis of the data did not allow to highlight any effect either in terms of mortality (OR 0.90; 95% 0.70-1.12), or of the use of mechanical ventilation (OR 0. 89; 0.76-1.03), or time to improvement clinical (9.0 in the SOC group vs 11.0 days in the remdesivir group; average difference of -2 days; 95% CI -4.2 to +0.9), or duration of hospitalisation (12.8 in the SOC group vs 12. 3 in the remdesivir group; average difference of -0.5 days; 95% CI -3.3 to +2.3)
- In one of the available living systematic reviews, edited by the Cochrane group in collaboration with numerous universities and research institutes (https://covid-nma.com/living_data/index.php), the analysis of the available data, updated to 09/12/2021, confirms the substantial absence of clinical benefit of remdesivir in terms of mortality at 28 days in hospitalized subjects (RR 0.92; 95% CI 0.78-1.07).

In conclusion, the main randomized studies that evaluated the clinical efficacy of remdesivir in the treatment of hospitalized subjects, albeit open and with different primary endpoints, show consistent results in excluding a clinical benefit of remdesivir in terms of mortality. A positive effect in terms of time to recovery is confirmed in a single study, especially in the lower-risk population (subjects receiving low-flow oxygen therapy and starting treatment within 10 days of the onset of symptoms).

Recommendations of international organisations

Subjects not hospitalised for COVID-19

- ***Infectious Diseases Society of America (IDSA)*** *(last updated 23/12/2021)*: In outpatients with mild-to-moderate COVID-19 and at high risk of progression to severe disease, the expert panel suggests starting remdesivir within seven days of symptom onset (conditional recommendation; lowcertainty of evidence) .
- **National Institutes of Health (NIH):***(last updated 23/12/2021):* in non-hospitalized subjects with mild-moderate COVID-19 and at high risk of progression, the panel of experts recommends the use of remdesivir.

Subjects hospitalised for COVID-19

- ***Infectious Diseases Society of America (IDSA)*** *(last updated 23/12/2021)*:
    - In hospitalised patients with severe COVID-19 (with SpO2 ≤94% in ambient air), the expert panel suggests the use of remdesivir (Conditional recommendation, moderate level of certainty of evidence).
    - In patients with COVID-19 undergoing invasive ventilation and/or ECMO, the expert panel suggests not starting remdesivir routinely (Conditional recommendation, very low level of certainty of evidence).
    - In patients on supplemental oxygen therapy but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, low certainty of evidence).
    - In COVID-19 patients admitted to hospital without the need for supplemental oxygen and oxygen saturation> 94% on ambient air, the IDSA panel of experts suggests not starting remdesivir routinely. (Conditional recommendation, very low level of certainty of evidence).
- **National Institutes of Health (NIH):)** *(last updated 16/12/2021)*: The panel of experts strongly recommends (with grade BII recommendation) treatment with remdesivir of hospitalized subjects on

low-flow oxygen therapy. The use, in combination with dexamethasone, in hospitalized cases with high-dose oxygen supplementation or in non-invasive mechanical ventilation is recommended with grade BIII recommendation.

- ***World Health Organization (WHO)*** *(last updated 24/09/2021)*: The panel of experts does not recommend the use of remdesivir in the treatment of patients hospitalised for COVID-19 regardless of the disease severity stage (weak or conditional recommendation). Currently available evidence does not suggest any important effect on mortality, on the need for mechanical ventilation, or on time to clinical improvement. The panel considered that the subgroup analyses show degrees of uncertainty that are too high to evaluate the reliability of the results, in consideration of important methodological problems (absence of a specific hypothesis of direction of the effect in the different subgroups, few or none pre-existing evidence to support the results obtained, arbitrariness of the cut-offs used to identify the different subgroups, presence of bias and methodological limitations that respond overall to a low quality of evidence). The panel, despite the conditional recommendation against the use of remdesivir, supports further enrollment of subjects in RCTs that use remdesivir, to provide greater certainty of evidence relating, particularly to specific subgroups of patients.

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