NEW DRUGS

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Remdesivir

Approved indication: COVID-19

Veklury (Gilead)
vials containing 100 mg powder or 100 mg/20 mL concentrate

Remdesivir, an antiviral originally designed to target the Ebola virus, has been provisionally approved for COVID-19. It is indicated for adults and adolescents with pneumonia who require supplemental oxygen. Remdesivir is a nucleotide analogue that delays replication of viral RNA. It comes in the form of a prodrug which is metabolised to the active form (remdesivir triphosphate) once it enters cells. In vitro studies have shown that it has antiviral activity against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1]

There have been several studies of remdesivir in hospitalised patients with COVID-19. These have included a compassionate use program,[2] two placebo-controlled trials[3,4] and two dosing trials[5,6] (see Table). Apart from the placebo-controlled trial in China,[4] all of these studies are ongoing and results are preliminary.

The studies enrolled patients with severe disease and an oxygen saturation of 94% or less, except the unpublished dosing trial which enrolled patients with moderate disease.[6] All except the dosing studies included (some) patients who required mechanical ventilation. Trials assessed a 10-day intravenous course of remdesivir starting with a loading dose of 200 mg on day 1 followed by 100 mg on subsequent days. The two dosing trials compared a 10-day course with a 5-day course of remdesivir.[5,6]

The Adaptive COVID-19 Treatment Trial found that patients receiving remdesivir recovered faster than those receiving placebo (median of 11 days vs 15 days).[3] However, in the Chinese placebo-controlled trial, remdesivir was not associated with a statistically shorter time to clinical improvement compared to placebo (median 21 days vs 23 days). This trial was terminated early due to control of the outbreak, therefore its statistical power was reduced from 80% to 58%.[4]

The dosing trials[5,6] compared a 5-day course of remdesivir with a 10-day course. One of the trials reported no statistical difference in clinical benefit between the two durations. There was no placebo arm in this trial so the magnitude of the clinical benefit could not be quantified.[5]

The other dosing trial[6] included a standard of care arm as a control. Enrolled patients were hospitalised with moderate disease (pneumonia without reduced oxygen saturation). At 11 days, clinical improvement was statistically better in patients who received the 5-day course, but not the 10-day course, compared to standard of care (see Table). These results have not yet been published in a peer-reviewed journal.

In terms of safety, increased liver enzymes are very common with remdesivir. It is therefore not recommended in people with elevated alanine aminotransferase (≥5 times the upper limit of normal). Headache, nausea and rash were common adverse events in the trials.

Remdesivir is a category B2 drug in pregnancy. Over 300 pregnant women have received it through a compassionate use program but there are no safety data available from this so far. Animal studies show that a metabolite of remdesivir is excreted in breastmilk.

Remdesivir is administered by an intravenous infusion. Peak plasma concentrations are reached 1.5–5 hours after the start of the infusion. Most of the dose is excreted as metabolites in the urine (74%) and faeces (18%). This product contains the excipient sulfobutyl betadex sodium which is renally cleared. As this accumulates in people with impaired kidney function, remdesivir is not recommended when the estimated glomerular filtration rate is less than 30 mL/min.

Drug–drug interaction studies have not been carried out with remdesivir so the potential for interactions is not known. In vitro studies suggest that strong inhibitors and inducers of cytochrome P450 (CYP) enzymes 2C8, 2D6 and 3A4 may affect remdesivir plasma concentrations. Concomitant hydroxychloroquine or chloroquine is not recommended due to possible antagonism.

Remdesivir seemed to be marginally better than placebo or standard of care in patients with severe COVID-19 in some of the clinical trials but not others. However, clinical data are limited and most results are preliminary. More comprehensive evidence of benefit is awaited by the Therapeutic Goods Administration. At this stage, the Australian guidelines for the clinical care of people with COVID-19 give a conditional recommendation for remdesivir stating that, where possible, remdesivir should be used in the context of a clinical trial but can be considered outside of a trial setting for patients with moderate, severe and critical COVID-19. However, they do warn against its routine use in pregnant and lactating women outside of a trial.

TT manufacturer provided additional useful information

Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table **Efficacy of the antiviral remdesivir* for severe COVID-19**

Trial	Study arms	Efficacy	Mortality
Compassionate use program (single-arm)[2]	Remdesivir for 10 days (53 patients)	Clinical improvement in terms of oxygen requirement: 68% of patients improved, 15% got worse	13% after a median of 15 days of treatment
Placebo-controlled trial (Adaptive COVID-19 Treatment Trial)[3]	Remdesivir (538 patients) vs placebo (521 patients) for 10 days	Median time to recovery:† 11 vs 15 days (rate ratio 1.32, CI 1.12–1.55 P<0.001)	7.1% vs 11.9% at 14 days (HR 0.7, CI 0.47–1.04)
Placebo-controlled trial (in Hubei, China) ††[4]	Remdesivir (158 patients) vs placebo (78 patients) for 10 days	Median time to clinical improvement: 21 vs 23 days (HR 1.23, CI 0.87–1.75)	14% vs 13% at 28 days
Open-label, randomised dosing trial ‡[5]	Remdesivir for 10 days (197 patients) vs 5 days (200 patients)	Clinical improvement of 2 points on a 7-point scale:§ 54% vs 65% Median time to recovery: 11 vs 10 days	11% (10 days) vs 8% (5 days)
Open-label, randomised dosing trial with standard of care arm #[6]	Remdesivir for 10 days (193 patients) vs 5 days (191 patients) vs standard of care (200 patients)	Clinical improvement on a 7-point scale§ compared to standard of care at day 11: • 5-day course – OR 1.65 (CI 1.09–2.48, p=0.17) • 10-day course – OR 1.31 (CI 0.88–1.95, p=0.18)	1% (10 days) vs 0% (5 days) vs 2% (standard of care)

CI confidence intervals, HR hazard ratio, OR odds ratio

* Patients received a loading dose of 200 mg on day 1 followed by 100 mg a day after that.

† Recovery defined as hospital discharge or hospitalisation for infection control purposes only.

†† Concomitant treatments for COVID-19 were allowed including lopinavir/ritonavir, interferons and corticosteroids.

‡ Patients receiving mechanical ventilation were not included in this trial.

§ 1=death, 2=hospitalised and receiving invasive ventilation, 3=hospitalised receiving non-invasive ventilation or high-flow oxygen, 4=hospitalised receiving low-flow oxygen, 5=hospitalised with no oxygen requirement but needing medical care, 6=hospitalised with no oxygen or medical care needed, 7=not hospitalised

\# Patients had moderate disease (pneumonia without reduced oxygen saturation).

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.