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INVESTIGATION

Covid-19: EU countries spent over €220m stockpiling remdesivir despite lack of effectiveness, finds investigation

The drug's manufacturer was aware of the negative results of the Solidarity trial before the European Commission struck a procurement deal with it, finds an investigation by Lucien Hordijk and Priti Patnaik

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On 7 October the European Commission struck a so called joint procurement framework deal with the drug manufacturer Gilead, after reports the day before of shortages of the antiviral remdesivir in the UK,[1] the Netherlands,[2] Spain, and Poland.[3] The EC agreed to buy 500 000 treatment courses in six months for €1bn (£0.9bn; $1.2bn). Though not all this money has been spent yet, 36 participating European countries (inside and outside the European Union) have collectively already purchased more than 640 000 vials, costing €220m. The countries' volume of orders differs considerably (box 1), although under the agreement all have to pay €345 per vial, or on average €2070 for a course of treatment.[4]

Box 1: What countries bought

The BMJ contacted the governments of the 36 countries participating in the remdesivir deal and was able to obtain information on orders from 17.

- Portugal ordered 100 000 vials, while Germany purchased 155 000, despite having a population eight times that of Portugal and just half the infection rate.[1]
- Spain, which was severely struck by the first wave of the pandemic and experienced shortages of remdesivir in late September, said it had ordered 15 000 vials.
- France and Luxembourg have stopped ordering the product altogether.
- Other countries, such as the Netherlands, Denmark, and Austria, say their orders are confidential.
- The UK is part of the scheme but did not disclose the number of doses ordered.

The deal was made just eight days before the World Health Organization's Solidarity trial into potential treatments for people with covid-19 made public its interim results on 15 October (box 2). These showed that among patients in hospital remdesivir had no effect on mortality, length of stay, or need for ventilation.[11]

Box 2: Remdesivir timeline

- 18 March 2020: WHO launches the Solidarity therapeutics trial, with remdesivir as one of the drugs.
- 29 April: A study from Wuhan, China, published in the *Lancet*, concludes that "remdesivir was not associated with statistically significant clinical benefits."[5] On the same day the US National Institutes of Health issues a statement about early and unpublished results from the Adaptive COVID-19 Treatment Trial (ACTT), an international trial funded by the National Institute of Allergy and Infectious Diseases. The NIH claims the study showed that patients with advanced covid-19 who received remdesivir recovered faster than patients who received a placebo.[6]
- 1 May: Remdesivir gets emergency use approval from the US Food and Drug Administration.
- Mid-May: Gilead signs voluntary licensing deals on remdesivir for distribution in 127 countries.
- 22 May: Preliminary results from the ACTT study are published in *NEJM*.[7]
- 29 June: The Trump administration orders almost all of the global stock of remdesivir for three months.
- 3 July: Remdesivir receives a conditional approval from the European Medicines Agency.
- 30 July: An international guideline panel makes a weak recommendation for the use of remdesivir in severe covid-19 in *The BMJ*'s Rapid Recommendations series.[8]
- 28 August: FDA expands emergency use authorisation for remdesivir.[9]
- Late September: Gilead receives a manuscript of the interim results from the WHO Solidarity trial, which show that remdesivir had little or no effect on hospital patients with covid-19.
- 6 October: The media report shortages of the drug in the EU.
- 7 October: The European Commission signs a joint procurement framework agreement for 500 000 treatments, for €1035bn.
- 8 October: Full results from ACTT are published in *NEJM*.
- 14 October: The EC notifies participating countries that they can order remdesivir as they see fit; no allocation key is needed any more because Gilead is able to fulfil demand completely.
- 15 October: WHO announces the interim Solidarity trial results showing a lack of effectiveness and uploads a preprint at MedRxiv.
- 15 October: Remdesivir is put on WHO's prequalifications list.
- 22 October: FDA approves remdesivir for the treatment of covid-19.
- 20 November: WHO recommends against the use of remdesivir, as more results from the Solidarity trial emerge. In *The BMJ* a WHO group states that

remdesivir "has no meaningful effect on mortality or on other important outcomes for patients, such as the need for mechanical ventilation or time to clinical improvement."[10]

- 20 November: WHO suspends remdesivir from its prequalifications list.
- 20 November: WHO clarifies that the remdesivir arm of the Solidarity trial continues, saying that final data from the trial will be shared with other regulators soon.
- 20 November: EMA says it will evaluate new data from the Solidarity trial.

Marie-Paule Kieny, a French virologist and member of the WHO Solidarity executive group, confirmed that Gilead was aware of the results. "WHO had an obligation to send Gilead the manuscript with the results before publication. This is standard practice, since the Solidarity trial was testing its molecule," she told *The BMJ*.

Gilead acknowledged that WHO shared the Solidarity results with it in late September but said the manuscript was "heavily redacted, highly confidential, and incomplete." However, a WHO spokesperson said that only information on other drugs was blacked out in the initial report, as is standard practice. Gilead declined to comment further about what was redacted. It said that it was not entitled to share the information about remdesivir's poor performance in the trial with the EC before the results were made public on 16 October.

The journal *Science* reported that the EC was unaware of the results when it struck the deal with Gilead on 7 October.[5] And an EC spokesperson confirmed to *The BMJ* that "the commission did not discuss this issue with Gilead prior to the publication of the preliminary WHO Solidarity trials." However, Gilead said it had "heard" that the EC had been informed of the results before 7 October, through member states.

The company has aggressively disputed the Solidarity trial results, insisting that the safety and efficacy data for remdesivir "remained strong."

Procurement process questioned

Brook Baker, professor of law at Northeastern University in Boston, believes the contract may have been poorly negotiated. "The question for the European Commission is: why did it not have a contract with Gilead with an escape clause based on the Solidarity trial outcome?" he said. "Regulators and authorities have an ongoing responsibility to ensure safety and efficacy."

Critics urged the EC to at least revisit the deal when negative results emerged from the Solidarity trial.[12] An EC spokesperson declined to comment on whether there were specific clauses in the contract, though another official said the framework does not allow for renegotiation.

Regulation in a pandemic

The case of remdesivir also raises questions about WHO's regulatory processes in the context of a pandemic. WHO has a prequalification system that essentially assesses the quality and safety of potential products to allow countries to procure a drug or vaccine through the international supply system. But experts have questioned whether this process is sufficiently aligned with WHO's clinical guidance.

WHO's prequalification team approved remdesivir for listing on 15 October, the same day the Solidarity trial results were made public that showed its lack of effectiveness. And it took until 20 November to suspend the listing for remdesivir, only after WHO issued a "conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity."[13]

A WHO spokesperson said the processes concerning prequalification and the Solidarity trials were strictly separated, to avoid conflicts of interest. The initial listing was based on the conditional approval given by the European Medicines Agency in July, the spokesperson added.

Baker said, "WHO's prequalification team was apparently sitting there without being well connected to the wider WHO clinical guidance and to expert networks and advice. It is not clear why WHO went ahead and prequalified the drug, despite emerging evidence against its effectiveness. It uncritically accepted the conditional marketing authorisation by the EMA."

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