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April 21, 2021

Janet Woodcock, M.D.
Acting Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Ave
Silver Spring, MD 20993

Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Acting Commissioner Woodcock and Director Cavazzoni:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly disagree with the Food and Drug Administration's (FDA's) inexcusable failure to refer the new drug application (NDA) for remdesivir (VEKLURY) to the agency's Antimicrobial Drugs Advisory Committee prior to approving the drug on October 22, 2020, for adult and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization.¹

That the FDA negligently avoided seeking advisory committee input is documented by the fact that prior to approving remdesivir, the agency had reviewed an October 15, 2020, preprint article that presented interim results of the World Health Organization (WHO) Solidarity trial, which was subsequently published in the *New England Journal of Medicine* online on December 2 and in print on February 11.² That large, multicenter, randomized clinical trial seriously challenged the FDA's conclusion that remdesivir is effective as a treatment for COVID-19. The WHO Solidarity trial investigators concluded, "Remdesivir... appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay."³

¹ Food and Drug Administration. Letter to Gilead Sciences, Inc., approving NDA 214787. October 22, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf. Accessed April 19, 2021.

² WHO Solidarity Trial Consortium, et al. Repurposed antiviral drugs for Covid-19 — interim WHO Solidarity Trial results. *N Eng J Med*. 2021;384(6):497-511.

³ WHO Solidarity Trial Consortium, et al. Repurposed antiviral drugs for Covid-19 — interim WHO SOLIDARITY trial results. <https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1>. Accessed April 19, 2021.

We therefore urge you to promptly convene a meeting of the FDA's Antimicrobial Drugs Advisory Committee to evaluate all currently available evidence regarding the safety, efficacy, and real-world effectiveness of remdesivir and to consider whether the approval of the drug should be rescinded.

Background on statutory requirements for convening FDA advisory committee meetings prior to approval of new drugs

Section 505(s) of the Food, Drug, and Cosmetic Act (FDCA; 21 U.S.C. 355(s)) requires the following:

Prior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of title 42, the Secretary shall-

(1) refer such drug to an FDA advisory committee for review at a meeting of such advisory committee; or

(2) if the Secretary does not refer such a drug to an FDA advisory committee prior to the approval of the drug, provide in the action letter on the application for the drug a summary of the reasons why the Secretary did not refer the drug to an advisory committee prior to approval.

Under section 505(n) of the FDCA (21 U.S.C. 355(n)), a major purpose of FDA advisory committees is to provide independent expert scientific advice and recommendations to the agency regarding the approval for marketing of a drug.

Historically, the FDA has routinely referred to its advisory committees first-in-class new drugs prior to their initial approval for marketing. Moreover, the public-at-large, including members of the U.S. Congress, have come to regard advisory committee review as a critical step in the FDA's evaluation of complex or high-profile NDAs. One group of seven U.S. senators recently wrote in a letter to President Biden, "The FDA convenes an advisory committee of scientific experts when a matter is of significant public interest, highly controversial, or in need of a specific type of expertise."⁴ Consideration of the first purported drug therapy for a deadly global pandemic disease very plausibly checks all three of these rationales for convening an advisory committee meeting.

FDA's unacceptable decision not to refer the NDA for remdesivir to the Antimicrobial Drugs Advisory Committee prior to approval

The FDA decided not to refer the NDA for remdesivir to the Antimicrobial Drugs Advisory Committee prior to approving the drug in October 2020. The approval letter to Gilead Sciences, Inc., for remdesivir included the following boilerplate text explaining the agency's decision:

⁴ Manchin J, Hassan MW, King AS, et al. Letter to President Biden regarding the ongoing opioid epidemic. March 26, 2021.

<https://www.manchin.senate.gov/imo/media/doc/210326%20Letter%20to%20WH%20Re%20FDA%20Opioids.pdf>.

Accessed April 19, 2021.

Your application for VEKLURY was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for the drug in the intended population and did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.⁵

This stated rationale that an advisory committee was not needed because the application did not raise significant efficacy issues was directly refuted by the lack of substantial evidence of effectiveness for remdesivir in the WHO Solidarity trial. As such, it is unacceptable that the agency evaded seeking input from the independent experts on the Antimicrobial Drugs Advisory Committee and from the public through the open public hearing that would have been part of an advisory committee process, particularly when the drug in question already was being made widely available to patients in the U.S. under an Emergency Use Authorization (EUA) granted on May 1, 2020.⁶

The main beneficiary of the highly debatable decision to approve remdesivir seems to be Gilead Sciences, which presently is earning massive, monopoly-protected profits⁷ thanks to the premature full approval by the FDA. Notably, unlike the COVID-19 vaccines, which all require vetting by the FDA's Vaccine and Related Biological Products Advisory Committee prior to the issuance of an EUA, remdesivir was granted full approval status without any such independent expert input.

Efficacy data included in the initial NDA for remdesivir

FDA approval of remdesivir was based on five clinical trials, three formally submitted as part of the sponsor's NDA, and two third-party studies. The FDA reviewers described marginal and sometimes confusing results from these trials, but they still somehow determined that the "overall benefit-risk profile of [remdesivir] is favorable"⁸ and that there was "substantial evidence of effectiveness."⁹ That insupportable conclusion thus far stands without advisory committee input, even as the FDA summary review noted that remdesivir "would be the first

⁵ Food and Drug Administration. Letter to Gilead Sciences, Inc., approving NDA 214787. October 22, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2020/214787Orig1s000ltr.pdf. Accessed April 19, 2021.

⁶ Food and Drug Administration. Letter to Gilead Sciences, Inc., reissuing an Emergency Use Authorization for emergency use of remdesivir for the treatment of hospitalized COVID-19 patients younger than aged 12. October 22, 2020. <https://www.fda.gov/media/137564/download>. Accessed April 19, 2021.

⁷ Tribble, SJ. Remdesivir, given to halt of hospitalized Covid patients in the U.S., is big win for Gilead — Boosted by taxpayers. Kaiser Health News, January 27, 2021. <https://khn.org/news/article/remdesivir-given-to-half-of-hospitalized-covid-patients-in-u-s-is-big-win-for-gilead-boosted-by-taxpayers/>. Accessed April 19, 2021.

⁸ Food and Drug Administration, Center for Drug Evaluation and Research. Summary review. Application number: 214787Orig1s000. October 21, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000SumR.pdf. Accessed April 19, 2021.

⁹ Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review(s). Application number: 214787Orig1s000. September 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000MedR.pdf. Accessed April 19, 2021.

drug approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19.”¹⁰

The primary efficacy data that supported the FDA’s October 2020 approval of remdesivir came from the National Institute of Allergy and Infectious Diseases-sponsored pivotal phase 3 clinical trial designated as the Adaptive COVID-19 Treatment Trial (ACTT-1). Two trials sponsored by Gilead Sciences (trial identifiers: GS-US-540-5774 and GS-US-540-5773) also were used to evaluate remdesivir’s efficacy for this NDA.

ACTT-1

ACTT-1 (NCT04280705) was a multinational, randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of remdesivir in hospitalized patients with mild-to-severe COVID-19.¹¹ Subjects (n=1,062) were evenly randomized into a remdesivir or a placebo group, receiving such therapy for up to 10 days. The primary efficacy endpoint of this trial was time to recovery through day 29, based on an eight-point ordinal scale ranging from discharge with no limitation on activities (score=1) to death (score=8). A secondary outcome was mortality through day 29, though it notably was neither a pre-specified primary nor a key secondary endpoint of this trial.

ACTT-1 found that remdesivir exposure increased the 29-day recovery rate (recovery rate ratio 1.29; 95% confidence interval [CI]: 1.12,1.49; p< 0.001), corresponding to median days to recovery that favored remdesivir (10 days; 95% CI: 9,11) over placebo (15 days; 95% CI: 13,18) by only five days. A subgroup analysis showed that the improvement in the primary efficacy outcome with remdesivir versus placebo was only statistically significant for subjects requiring hospital-based medical care and supplemental oxygen but not those with more severe (requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]).

Mortality results for ACTT-1 showed that at 29 days, 11% of the remdesivir-group subjects had died versus 15% of the placebo-group subjects, a difference that was not statistically significant [hazard ratio 0.73; 95% CI: 0.52,1.02; p=0.066].

Based on these data, the FDA clinical reviewers concluded that the “trial provided reliable and statistically persuasive evidence of benefit for [remdesivir] in hospitalized patients with COVID-19.” The statistical reviewers concurred with that conclusion but noted that the data for remdesivir’s efficacy in reducing mortality overall and morbidity or mortality in the subjects with the most severe COVID-19 were “inconclusive.”

¹⁰ Food and Drug Administration, Center for Drug Evaluation and Research. Summary review. Application number: 214787Orig1s000. October 21,2020.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000SumR.pdf. Accessed April 19, 2021.

¹¹ *Ibid.*

Trial GS-US-54-5774

Trial GS-US-540-5774 (NCT04292730) was a multinational open-label trial that randomized 584 hospitalized subjects with moderate COVID-19 into one of three groups: five days of remdesivir, 10 days of remdesivir, or standard of care. The primary endpoint was clinical status on day 11 based on a seven-point ordinal scale ranging from death (score=1) to not hospitalized (score=7).¹² Moderate COVID-19 was defined as being hospitalized with laboratory-confirmed SARS-CoV-2 infection, radiographic evidence of pulmonary infiltrates, and oxygen saturation >94% on room air; patients with mechanical ventilation at screening were excluded. According to the FDA, this trial provided supportive evidence for the efficacy of remdesivir in patients with moderate COVID-19 illness, a group that made up a small proportion of the subject population (10%) enrolled in ACTT-1.¹³

The odds of improvement at 11 days for the five-day remdesivir group versus placebo was statistically significant (odd ratio [OR] 1.59; 95% CI: 1.00, 2.51; p=0.05), but statistically significant improvement was not seen for the 10-day course of the drug (OR=1.15; 95% CI: 0.75, 1.79; p=0.52). Corresponding rates of hospital discharge (fullest recovery measured) were 71%, 65%, and 62% for five-day remdesivir, 10-day remdesivir, and standard-of-care groups, respectively. No significant impact on mortality was evident as only two deaths in the entire trial occurred, both in the 10-day remdesivir group.

The overall assessment of the FDA clinical and statistical reviewers was that five-day remdesivir demonstrated significant time-to-recovery efficacy versus standard of care and that the 10-day course indicated a trend in that direction. FDA reviewers further noted that the open-label design of the trial may have biased the results against a significant 10-day effect because that course may have caused subjects to remain in the hospital longer than necessary.

Nevertheless, the failure to see a statistically significant improvement on the efficacy outcome for the 10-day course of remdesivir raises doubts about whether the drug provides clinically meaningful benefit for subjects with moderate COVID-19. Moreover, the open-label design arguably creates considerable bias in favor of remdesivir's efficacy, given the commercial and humanitarian hopes that naturally surrounded such a widely anticipated treatment.

Trial GS-US-540-5773

Trial GS-US-540-5773 (NCT0429899) was a multinational, open-label trial that evenly randomized 397 subjects with severe COVID-19 cases to receive either a five-day or 10-day course of remdesivir. A major limitation of this trial was the lack of a placebo or standard-of-care control group. Severe COVID-19 in this study was defined as being hospitalized with laboratory confirmed SARS-CoV-2 infection, radiographic evidence of pulmonary infiltrates, and oxygen saturation levels ≤94% on room air or requirement for supplemental oxygen. The

¹² *Ibid.*

¹³ Food and Drug Administration, Center for Drug Evaluation and Research. Statistical review(s). Application number: 214787Orig1s000. August 7, 2020.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000StatR.pdf. Accessed April 19, 2021.

primary endpoint was clinical status at day 14 on the same seven-point ordinal scale used for trial GS-US-540-5774.¹⁴

The trial found no statistically significant difference between the five-day and 10-day remdesivir groups with adjustment for differences in baseline on the primary efficacy outcome of clinical status at day 14, although the odds ratio for this outcome nominally favored the five-day course (OR 0.74; 95% CI: 0.5, 1.1; p=0.14).

Notably, a larger proportion of the 10-day remdesivir group subjects either died by day 14 or required invasive mechanical ventilation or ECMO on day 14 than did the five-day remdesivir subjects (28% versus 17%, respectively). Additionally, more 10-day remdesivir group subjects had either died or were receiving invasive mechanical ventilation or ECMO at day 28 compared with the five-day remdesivir subjects (23% versus 15%, respectively). Finally, more subjects in the 10-day remdesivir group discontinued treatment for nonfatal adverse events than those in the five-day remdesivir group (11% versus 5%, respectively).

The FDA clinical reviewers commented that the apparent trend toward better outcomes in the five-day remdesivir group may have been partially related to an imbalance in the baseline disease severity between the two groups; in particular, a significantly higher proportion of subjects in the 10-day remdesivir group required mechanical ventilation or high-flow oxygen at baseline.

The reviewers' overall assessment was that the results from this trial were "suggestive of a similar treatment effect with five-day and 10-day regimens in [the studied] population."¹⁵ However, due to the lack of a control group, the magnitude of benefit could not be determined. Moreover, the conclusion was made that a five-day treatment course of remdesivir is sufficient, without acknowledging that the 10-day regimen in this trial nominally performed worse than the 5-day course on many important indicators.

Third-party trials

The FDA reviews of remdesivir also included discussion of two third-party clinical trials: a randomized, placebo-controlled trial conducted in China and the WHO's Solidarity trial.

Wang et al. (CO-US-540-5758; NCT04257656)

The FDA clinical and statistical reviews referenced an investigator-sponsored, randomized, double-blind, placebo-controlled clinical trial conducted in China that enrolled subjects with severe COVID-19 (within 12 days of illness onset, pneumonia confirmed by chest imaging, and oxygen saturation $\leq 94\%$ on room air or a partial oxygen pressure/fraction of inspired oxygen

¹⁴ Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review(s). Application number: 214787Orig1s000. September 16, 2020.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000MedR.pdf. Accessed April 19, 2021.

¹⁵ *Ibid.*

ratio ≤ 300 mm Hg).^{16,17,18} The primary outcome assessed was time to clinical improvement up to day 28 after randomization. Because public health measures in China controlled case rates so well, the trial was terminated before it could enroll the planned 453 subjects. Instead, only 237 subjects were enrolled and randomized to receive a 10-day course of either remdesivir (158 subjects) or a placebo (78 subjects).

The median time to clinical improvement was 21 days for the remdesivir group and 23 days for the placebo group, a difference that was not statistically significant (HR 1.23; 95% CI: 0.87, 1.75; $p=0.24$). The proportion of subjects with at least a two-point improvement on the six-point clinical status scale (death to hospital discharge) by day 28 was 65% in the remdesivir group versus 58% in the placebo group, a difference that also was not statistically significant (7.5%; 95% CI: -6, 20). In addition, the trial again revealed no mortality benefit as 14% of the remdesivir-group subjects died compared with 13% of the placebo-group subjects.

Although these efficacy findings were not statistically significant, the FDA statistical reviewers concluded that because this trial was much smaller than ACTT-1, there was a higher degree of uncertainty in estimating treatment effects. They further noted that “the point estimate for the remdesivir treatment effect was consistent with results from the adequate and well- controlled ACTT-1 using a similar time to improvement endpoint for the primary analysis. Thus, this trial was not considered to have provided discordant findings.” A more appropriate assessment should have emphasized that the Chinese trial was uninformative because it enrolled only 237 of 453 needed subjects.

WHO Solidarity trial

The WHO Solidarity trial (NCT04315948) provided additional data that seriously challenges the FDA’s conclusion that remdesivir is effective as a treatment for COVID-19. This trial used a randomized, open-label design that has involved up to five treatment arms (remdesivir, hydroxychloroquine, lopinavir, interferon beta-1a and local standard of care). Interim results from the trial were received by the FDA prior to approval and subsequently published online by the *New England Journal of Medicine* on December 2, 2020, and in print on February 11, 2021.¹⁹

The WHO Solidarity trial was conducted in 405 hospitals across 30 countries and the published analysis included randomized assignment of 2,750 adults to remdesivir and 2,708 to local standard of care. The primary outcome was in-hospital mortality. The only protocol-specified secondary outcomes were the initiation of mechanical ventilation and duration of hospital stay. Death occurred in 301 subjects in the remdesivir group and 303 subjects in the control group (rate ratio= 0.95, 95% CI: 0.81 to 1.11). For the prespecified secondary outcomes, remdesivir did

¹⁶ *Ibid.*

¹⁷ Food and Drug Administration, Center for Drug Evaluation and Research. Statistical review(s). Application number: 214787Orig1s000.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000StatR.pdf. Accessed April 19, 2021.

¹⁸ Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578.

¹⁹ WHO Solidarity Trial Consortium, et al. Repurposed antiviral drugs for Covid-19 — interim WHO Solidarity Trial results. *N Eng J Med*. 2021;384(6):497-511.

not reduce the rate of mechanical ventilation or shorten the duration of hospitalization. Notably, mechanical ventilation initiation occurred in 295 (11%) of the remdesivir-group subjects and 284 (10%) of the control-group subjects receiving standard care.

Thus, this trial failed to show that remdesivir was effective in a real-world setting at decreasing mortality, mechanical ventilation initiation, or the duration of hospitalization, which are the key clinically meaningful outcomes in patients hospitalized with COVID-19.

In an October 22, 2020, addendum to the remdesivir NDA statistical review,²⁰ FDA statisticians made the following conclusion after reviewing a pre-print of the Solidarity preliminary results: “Collective results from the two trials [Solidarity and ACTT-1] are consistent with remdesivir having a neutral or small impact on all-cause mortality. While ACTT-1 results were suggestive of improved mortality, there remained residual statistical uncertainty, and the most straightforward interpretation of the two trials is that they have now ruled out a large mortality benefit.”

The five aforementioned studies led FDA reviewers to conclude that remdesivir should be moved from EUA to fully approved status. This evidence-denying decision was made without input from an advisory committee despite conflicting evidence from the trials regarding whether the drug provides clinically meaningful benefit.

Conclusions and requested action

The FDA’s decision not to refer the NDA for remdesivir (VEKLURY) to the agency’s Antimicrobial Drugs Advisory Committee prior to approving the drug on October 22, 2020, failed to meet the criteria for avoiding such a meeting. The statement that “the application did not raise significant safety or efficacy issues” amounts to a wrongful dismissal of the evidence against remdesivir’s effectiveness.

We therefore strongly urge you to promptly convene a meeting of the FDA’s Antimicrobial Drugs Advisory Committee to evaluate all currently available evidence regarding the safety and effectiveness of remdesivir and to consider whether the approval of the drug should be rescinded. Potential actions that the advisory committee should consider recommending are the following:

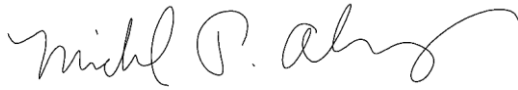
- Take remdesivir completely off the market because of a lack of substantial evidence that it is effective.
- Rescind the approval of remdesivir but allow it to remain on the market only under a much more limited EUA unless its safety and efficacy can be established.

²⁰ Food and Drug Administration, Center for Drug Evaluation and Research. Statistical review(s). Application number: 214787Orig1s000.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000StatR.pdf. Accessed April 19, 2021.

Thank you for your attention to this important public health issue.

Sincerely,



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