7 March 2023

Dr Mark Chakravarty

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Dear Dr Chakravarty,

**Final draft guidance – Therapeutics for people with COVID-19 – ID4038**

Executive summary

Gilead Sciences Ltd (**Gilead**) is appealing the final draft guidance (**FDG**) for the multiple technology appraisal (**MTA**) of therapeutics for people with COVID-19, on the following grounds:

Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

NICE has not followed its own published processes and methods and/or has acted unfairly:

1(a).1 For lack of time and resource allocated to this MTA, companies were not given the opportunity to make a full evidence submission and NICE refused Gilead’s request to submit an economic model, resulting in important evidence not being considered by the Committee.

1(a).2 For lack of time, the EAG relied on pre-existing living systematic reviews and network meta-analyses which were not originally designed to address the decision problem and were not sufficiently validated, resulting in significant flaws in the information considered by the Committee.

1(a).3 Cost-effectiveness estimates were not informed by a probabilistic sensitivity analysis without adequate justification, and so the Committee failed to sufficiently explore parameter uncertainty.

1(a).4 The Committee did not consider the cost-effectiveness of remdesivir for severe COVID-19 and so denied Gilead the opportunity to discuss commercial agreements that would mitigate or resolve the uncertainty around the ICERs.

1(a).5 The Committee did not conduct a thorough assessment of treatments for children with severe COVID-19 and the resulting failure to recommend any treatment for children with severe COVID-19 is unfair and discriminatory.

1(a).6 The Committee has not given any adequate reasons for not addressing the distinction between patients with severe COVID-19 on low-flow oxygen and those on high-flow oxygen despite this clear distinction being made in current guidance.

1(a).7 Gilead was not given a fair hearing because it was not given the opportunity to discuss key issues at the appraisal committee meetings.

1(a).8 NICE treated Gilead unfairly compared to another stakeholder company by refusing to consider new data that could potentially change the Committee’s final conclusions.

1(a).9 The Committee has not given adequate reasons why differences in standard care give rise to significant concerns about the generalisability of SOLIDARITY data.

1(a).10 The Committee’s exclusion of treatment effects for hospital time to discharge data for remdesivir is unfair because these treatment effects were reflected in the base-case ICER results for tocilizumab.

Ground 2

2.1 The Committee’s conclusion that significant uncertainty remains in terms of generalisability of the trial evidence for remdesivir in severe COVID-19 is unreasonable because it ignores clinical practice and in-vitro data that has not been countered.

2.2 The Committee’s recommendations are unreasonable because, ignoring clinical need and practice, they fail to recommend any antiviral treatment for patients with severe COVID-19.

## Introduction

The scope of the current MTA is highly ambitious, applying across both hospital and non-hospital settings, covering antiviral and anti-inflammatory approaches against an evolving disease and standard of care. In view of this scale, complexity, the heterogeneity of the underlying data and the use of novel methods, the MTA required investment of significant time and resource in order to develop a fair procedure and deliver a scientifically and clinically credible conclusion.

Unfortunately, NICE manifestly allocated insufficient time and resource to the MTA and has conducted a resource constrained and over-rapid process. As a result, the MTA has been the subject of a series of procedural errors and omissions. By way of example, the absence of full company submissions, a fundamental component of a robust technology appraisal, has meant that the MTA is essentially unanchored, adding deeper uncertainty to an already challenging process***.*** The MTA as a whole has been rushed and with inadequate efforts made to seek Gilead input.

Cumulatively, the series of procedural errors and omissions of the MTA have ultimately resulted in an incorrect conclusion regarding the cost-effectiveness of remdesivir, which would effectively withdraw the product from the NHS, where it is currently benefitting patients (approximately 68,000 patients treated with remdesivir since July 2020) – to the prejudice of all stakeholders. This is most acutely illustrated in the context of children with severe COVID-19 for whom remdesivir is the only licensed treatment, but who, as a result of the Committee’s recommendations, would have no treatment available.

NICE’s conclusions are contrary to recommendations from around the world: the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the WHO and the US National Institute of Health (NIH) all recommend remdesivir for use in hospitalised patients.[1-4] The WHO guidelines confirm that, while surveillance is needed for SARS-CoV-2 strains with reduced susceptibility to remdesivir, until further data is available, there is no reason to believe that activity against known variants will be diminished.

The fact that an appraisal is challenging, or a rapid result is requested by stakeholders does not justify a rushed assessment, with an unfair procedure and methods which have neither been validated nor subject to sufficient consultation. Gilead therefore submits that this MTA should not have been conducted on an *accelerated* basis and should now be divided to consider the different types of products under separate appraisals, conducted in accordance with NICE’s published process guides and to appropriate standards of scientific rigor. This will produce a more robust recommendation that better reflects the complex evidence base, providing the time and depth to explore the decision problem in the way that is warranted.

## Procedural history of the appraisal

The outline below in Table *1* sets out the key events and documents referred to in this letter.

Table 1: Summary of the procedural history of the appraisal.

| **Date** | **Event** |
| --- | --- |
| January 2022 – April 2022 | **Consultation on scope:**   * 03/02/22: Consultee and commentator comment forms submitted. * 15/03/22: NICE informed stakeholders of its intention to resequence the steps of the MTA, starting the academic work to assess the clinical evidence and develop an economic model, without stakeholder submissions. * 14/04/22: Stakeholder information meeting. |
| 19 April 2022 | **Final scope for appraisal issued** |
| July 2022 | **Stakeholder review of EAG report (30/06/22):**   * 04/07/22: EAG report issued (04/07/22). * 05/07/22: Gilead receives the economic model (v2 04/07/22). * 14/07/22: NICE informed Gilead of the first set of calculation errors in the EAG economic model. * 29/07/22: Gilead’s response to EAG report raised concerns about the EAG’s approach. |
| August 2022 | **Stakeholder targeted evidence submissions**   * 01/08/22: Invitation to participate with option to submit a targeted evidence submission. * 19/08/22 and 22/08/22: NICE refused Gilead requests to submit an economic model and brief write-up. * 26/08/22: Gilead’s targeted evidence submission raised concerns about the NICE process. * 14/09/22: NICE confirms that there would be no technical engagement or further evidence submissions before ACM1. |
| 18 October 2022 | **First Appraisal Committee Meeting (ACM1)** |
| 27 – 28 October 2022 | **Follow up to ACM1**   * 27/10/22: NICE issues to consultees: EAG report v2 30/06/22; EAG report v3 03/10/22; EAG economic evaluation erratum 25/10/22; EAG model (v5.0 27/10/22). * 28/10/22: Gilead asks for clarification of the changes between the EAG model v5.0 and the previous EAG model. * 28/10/22 NICE confirm the EAG corrected several calculation errors and errors with input data. |
| November – December 2022 | **Consultation on draft guidance (DG)**   * 09/11/22: DG issued to consultees. * 17/11/22: EAG model (v5.1 post ACM1, 14/11/22) issued. * 30/11/22: NICE request EAG clarification for changes to the EAG model v5.1 compared to v5.0. * 07/12/22: Gilead’s response to consultation includes concerns with the appraisal process. |
| December – January 2022 | **Follow up to consultation:**   * 23/12/22 and 06/01/23: Gilead responds to requests for additional evidence. * 17/01/22 Report from In-Vitro Advisory Group issued. |
| 24 January 2023 | **Second Appraisal Committee Meeting (ACM2)** |
| 31 January 2023 – 13 February 2023 | **Follow up to ACM2**   * 31/01/23: NICE informed consultees of intended decision (including not recommending sotrovimab). * 10/02/23: Gilead submitted additional evidence and requests third appraisal Committee meeting. * 13/02/23: NICE informed consultees of intended decision (including recommending sotrovimab). |
| 14 - 21 February 2023 | **Final Draft Guidance (FDG) issued and published.**   * EAG additional analysis post NICE Appraisal Consultation Document (13/0/1/23) issued to consultees. |

Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

In this MTA, NICE has not followed its own published processes and methods and/or has acted unfairly, as further described below.

It is a fundamental part of a fair process that published procedures will be followed and Gilead was entitled to expect that this would be the case in the current appraisal.

1(a).1 For lack of time and resource allocated to this MTA, companies were not given the opportunity to make a full evidence submission and NICE refused Gilead’s request to submit an economic model, resulting in important evidence not being considered by the Committee

Companies were not given the opportunity to make a full evidence submission, contrary to paragraphs 1.3.1, 3.1.1, and 5.5-5.6 of NICE’s Process and Methods Manual (the **Manual**).[5] Although the Manual allows for certain differences between the process for single technology appraisals and multiple technology appraisals, companies must be invited to submit evidence, and that evidence must be considered.

NICE did invite companies to make a targeted evidence submission, limited to additional comments on the EAG model, details of additional evidence, confidential arrangements that would apply in routine commissioning and any equality issues. This procedure was, however, inconsistent with the process described at paragraph 1.3.1 of the Manual, which does not restrict the evidence on the technology or technologies being evaluated which may be submitted by the company and requires companies to *identify all evidence relevant to the evaluation, the technology or technologies being evaluated*. The process at paragraph 1.3.1 is important because it allows companies to present the evidence relating to their products in a way they consider to be appropriate. Its omission has resulted in substantial prejudice to Gilead.

In view of Gilead’s significant concerns regarding the EAG model, Gilead asked to submit an economic model on 19th August and again on 22nd August 2022. NICE rejected Gilead’s requests:

In the **first** rejection, by email on 19th August 2022, NICE explained that that: *An executable model, write up and comparison from Gilead will not be accepted as the company had an opportunity to highlight any concerns with the Assessment Group’s model during the consultation.*

However, allowing Gilead to submit evidence only after the EAG has explored the evidence and developed its model is unfair and not in accordance with the Manual. Evidence submission is usually a key opportunity for companies to provide input into how an EAG conceptualises and then develops its modelling: companies’ detailed evidence submission indicates the data that is available to inform the EAG model. By contrast, in this case, the EAG model was developed in advance of any evidence submissions by companies, so reducing the EAG’s ability to make significant changes to its approach in light of company input, especially given the time restrictions to which the EAG repeatedly refers in its report.

Also, in view of the flaws in the EAG’s approach (see Ground 1(a).2), the limited opportunity that Gilead had to comment on the EAG model or to provide other evidence later in the process did not compensate for this fundamental process failure.

In the **second** rejection, by email on 22 August 2022, NICE explained that: *Given the number of technologies included in this MTA it wouldn’t be feasible for the [E]AG or committee to review models from all the companies*.

Lack of time and resource are not adequate reasons for refusing to accept evidence from a company. If there were too many technologies included in the MTA, such that it was not feasible for the EAG or the Committee to consider submitted evidence as required by a fair procedure, this provides strong grounds for concluding that the appraisal should have been divided into separate MTAs, for example according to different types of products, setting or population. NICE’s response to Gilead’s request to submit an economic model is an example of how the scope of this MTA is too broad and the process was unduly rushed, to the prejudice of stakeholders, including patients and the NHS.

If permitted to submit an economic model, Gilead would have submitted a cost-effectiveness analysis incorporating all relevant evidence for remdesivir according to NICE methods (as set out in the Manual), and so provided important evidence and information. For example, Gilead would have:

* addressed the distinction between patients on low-flow vs high-flow oxygen. This would have demonstrated that remdesivir has better outcomes in patients on low-flow oxygen and so is more cost-effective in this setting. The EAG and the Committee did not do this: see Ground 1(a).6.
* conducted a probabilistic sensitivity analysis (**PSA**), as this is standard practice in any economic model submitted to NICE, in accordance with section 4.7 of the Manual. The EAG did not do this and so the Committee did not consider this important information: see Ground 1(a).3.

Gilead raised concerns about this procedure on multiple occasions, including in its consultee and commentator form (03 February 2023), its Gilead’s response to the EAG report (29 July 2022), its targeted evidence submission (25 August 2022) and its response to consultation on the draft guidance (**DG**) (07 December 2022).

This failure to allow companies to make full evidence submissions is part of a wider problem with this appraisal: from the early stages of the MTA process NICE made clear that it would only accept limited information from companies and did not enable companies to make the best plausible case for their treatments for COVID-19, contrary to the Manual (paragraph 5.5.6). For example:

Opportunities to discuss the change from a Single Technology Assessment (**STA**) to an extremely broad and complex MTA were limited, and points raised were not taken on board by NICE. Gilead raised its concerns about this – for example, raising the need for additional touchpoints to address the complexity of the MTA (03 February 2022 and 16 February 2022) – but these concerns were not addressed.

In March 2022, NICE resequenced the steps of the MTA, knowing that the EAG would have to develop its report without the benefit of stakeholder submissions.

Gilead raised general concerns about the opportunity for companies to contribute to the appraisal at several points during the process, including in its response to the first EAG report (29 July 2022).

1(a).2 For lack of time, the EAG relied on pre-existing living systematic reviews and network meta-analyses which were not originally designed to address the decision problem and were not sufficiently validated, resulting in significant flaws in the information considered by the Committee

The pre-existing living systematic reviews and network meta-analyses were not designed to address the decision problem and so the EAG’s reliance on these sources did not meet the requirements of the Manual.

The Manual requires*:*

*a systematic review of the relevant evidence relating to a technology should be done using a pre-defined protocol. This protocol should allow evidence to be included from all sources likely to inform the decision about using the technologies by the NHS… All evidence should be critically appraised, and potential biases must be identified.* (paragraph 3.3.4).

*evidence on outcomes should come from a systematic review, defined as systematically locating, including, appraising, and synthesising the evidence to give a reliable and valid overview of the data related to a clearly formulated question.* (paragraph 3.4.2).

In this MTA, instead of designing a systematic review to address a clearly formulated question or decision problem, the EAG relied on two pre-existing living systematic reviews. This approach was inconsistent with the requirements of the Manual and substantially impaired the quality of the EAG report.

The EAG recognised this issue several times, explaining that:

* *given the timelines of the project, the EAG could not follow best practice for systematically reviewing the clinical evidence relevant to the decision problem*. (EAG report v.3 3 October 2022 pp.26).
* [g]*iven the timescale of the project, where there was less than three months between the publication of the final scope and the report deadline, a literature review following best practice was not possible. Instead, a pragmatic, alternative approach was undertaken where evidence was taken from two living systematic reviews (supported by the COVID-NMA initiative and the metaEvidence initiative) in line with current best practice guidelines.* (EAG report v.3 3 October 2022 pp.12).
* *The two living systematic reviews have limitations… However, the time required to undertake a full systematic review were beyond the time scales of this accelerated multiple technology assessment*. *The EAG has therefore continued to rely on these sources…* (EAG additional analysis post NICE Appraisal Consultation Document 13 January 2023, paragraph 52, pp 35).

This approach substantially limited the EAGs ability to conceptualise a model according to the decision problem and its interpretation of the disease pathway. The EAG itself acknowledges this – for example with regard to potential subgroups of interest: the EAG explains that: [a] *consequence of the need to use data from the living systematic reviews was that there was reduced scope for the EAG to undertake nuanced analyses with a key limitation being that the EAG had to assume that all relative treatment effects were generalisable to different settings. This meant that for each intervention, the same treatment effects, either hazard ratios (HRs) or relative risks (RRs), were assumed to be applicable regardless of study characteristics which include: the age, perceived severity, vaccination status, and history of SARS-CoV-2 infection of patients; the SoC at that time; the geographical location; and the dosage of the intervention used. The EAG acknowledge that this assumption may be incorrect, which adds additional uncertainty to the clinical- and cost-effectiveness results.* (EAG report, 3 October 2022, pp.27).

See further Ground 1(a).5).

The EAG essentially operated within the constraints of an evidence synthesis that it did not specify itself.

The EAG did not have time to conduct appropriate quality checks on the third-party living system reviews and network meta-analyses

The EAG did not validate the network meta-analyses generated by the third-party: The EAG explain that[a]*ll data and evidence synthesis analysis were extracted from forest plots, tables and text generated by the COVID-NMA and metaEvidence web interface; checking of the extracted data by the EAG against the original RCT publications for accuracy could not be undertaken within the timescales of the project* (EAG report v3, 3 October 2022, paragraph 2.1.4 pp.28).

The EAG also explain that [t]*he EAG did not have the time to attempt to untangle the impact of differences between studies in terms of aspects such as the dominant SARS-CoV-2 variant, SoC, vaccination status, outcome definition, and age of participants and caution that the results may not be directly comparable between interventions. The EAG also did not have time to: validate the data within the living systematic reviews; to quality assess the component studies; or to remove studies that were not using the appropriate doses.* (EAG report v3, 3 October 2022, pp.26).

It is unacceptable to rely on an incomplete and unchecked review of the evidence as a basis for guidance and if this is all that can be accomplished within the short timelines permitted, an accelerated appraisal is patently inappropriate. Lack of time cannot justify omitting to undertake vital work to ensure the completeness, validity and reliability of the evidence submitted for neglecting crucial quality control and ultimately the issue of poor-quality guidance to the NHS. This is not only procedurally unfair to stakeholders, but the output is also of limited if any use.

Generally, the EAG did not have sufficient time to perform its role

Generally, the EAG suffered from lack of time in conducting its work. The EAG noted that: *the deadline set for the original EAG report sent to stakeholders was 30th of June 2022, allowing less than three months for the estimates of the clinical effectiveness of each intervention to be made, for the mathematical models to be adapted and run, the results to be interpreted and the report to be written*. (EAG report v.3, 3 October 2023 pp.19).

Consequently, there were significant errors in the EAG model that were not corrected before the first meeting. Over the course of the MTA NICE shared 6 major iterations of the EAG model, with various corrections and updates in between versions. Given that initially the outcomes from the NMA were linked incorrectly to the efficacy scenarios, this resulted in the model outputting incorrect cost-effectiveness estimates. Overall, the numerous iterations of the EAG model have undermined its credibility and the reliability of the results generated by this model.

Impact

Overall, while the Manual (paragraph 1.2.12) defines the EAG as *an independent academic group that reviews the evidence including any stakeholder submissions and the clinical and cost effectiveness or cost comparisons of the technology or technologies being evaluated*, in this MTA the EAG did not have adequate time to do this work.

Section 3.1.1 of the Manual emphasises that *to ensure that the guidance issued by NICE is appropriate and robust, the evidence and analysis, and their interpretation, must be of the highest standard possible and transparent*. As explained above, this standard has not been met in this MTA, notwithstanding the complexity of this MTA.

Gilead raised concerns about the EAG’s approach, including in its targeted evidence submission and in its response to consultation on the DG.

The Committee acknowledged certain limitations of the EAG’s approach (FDG section 3.10) and sought to address such limitations by relying on scenarios showing ‘mean efficacy’, ‘lower efficacy’ and ‘higher efficacy’ estimates: however, this approach was flawed and does not address the fact that, in view of the limitations highlighted by the EAG itself, the COVID-NMA is not sufficiently aligned to the NICE decision problem and consequently not appropriate for decision making in this instance.

Many of the issues identified by Gilead (including those presented in this letter) stem from the truncated time in which the preliminary evidence and modelling was developed. See for example Grounds 1(a).5, 1(a).6 and 1(a).10.

1(a).3 Cost-effectiveness estimates were not informed by a probabilistic sensitivity analysis without adequate justification and so the Committee failed sufficiently to explore parameter uncertainty

The Manual (paragraph 4.7.13) requires that *in general, scenario analyses should also be probabilistic. When only deterministic base-case or scenario analyses are provided, this should be justified.*

As set out below, the failure to conduct a probabilistic sensitivity analysis (**PSA**) in this appraisal is not adequately justified.

Reasons given by EAG

The EAG recognised that PSA should have been conducted, explaining that *probabilistic sensitivity analysis (PSA) is the most appropriate method for providing the most accurate estimation of the ICER, however this could not be undertaken within the timescales of the project.* (EAG report v.3 3 October 2022 para 3.4 pp 60).

The EAG also acknowledge one of the weaknesses of failing to conduct a PSA: *One limitation associated with the omission of PSA is that value of information analyses could not be conducted to assess the monetary implications of recommending an intervention that was not the most cost-effective and to put a ceiling on the expenditure of research addressing knowledge gaps. This is an area for future research.* (EAG report v.3 3 October 2022 para 3.4 pp 63).

The EAG has given two reasons for why PSA was not run (EAG additional analysis post NICE Appraisal Consultation Document 13 January 2023 para 5.1, pp. 34):

The first reason concerns *time constraints due to the need to use Excel’s SOLVER functionality in the community analyses*.

However, time constraints do not justify the exclusion of critical analysis and an incomplete and unfair procedure. This is a further demonstration of how the inappropriate acceleration of this MTA has resulted in a procedure that is of inadequate quality and falls far below NICE’s standards. It appears that the lack of time and resource has resulted in an important source of evidence being omitted from the Committee’s consideration.

The second reason mentions the *relative unimportance of PSA when there was such considerable uncertainty in the true efficacy values due to changing conditions*.

This is not a valid reason: PSA as a form of sensitivity analysis is exactly intended for cases where there are concerns around efficacy to let decision makers better understand how outcomes may vary when probabilistic distributions are assigned to uncertain parameters.

This second reason is also contrary to section 4.7.12 of the Manual, which states that *uncertainty around individual parameters is not a reason to exclude them from probabilistic analyses; rather, that uncertainty should be captured in the analysis*.

Reasons given by the Committee

In the FDG, the Committee stated that the *appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis* because the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise (FDG section 3.10). Instead, the Committee relied on scenarios run by the AG using the mean and the upper and lower confidence limits of each efficacy estimate, to characterise the uncertainty. This provided scenarios showing ‘mean efficacy’, ‘lower efficacy’ and ‘higher efficacy’ estimates (resulting in extreme positions if – for example – only lower efficacy scenarios were assessed).

While it is acknowledged that PSA would not have captured all types of uncertainty, conducting a PSA would, nevertheless have provided the Committee with further evidence upon which to consider the effectiveness of remdesivir and other therapies and to make an adequately informed decision.

The EAG also advised the Committee that the alternative approach to investigation of uncertainty (at least in relation to efficacy) using the lower and higher efficacy scenarios had limitations because this represented a different uncertainty to that in the evidence base; they represented uncertainty on the estimates in the trial and were therefore sensitive to the number of events in each trial, rather than the context in which the trial happened. Therefore, they would not be sensitive to changes in efficacy against new circulating variants of concern. (FDG section 3.10).

Impact

By failing to conduct PSA, the Committee has failed adequately to investigate the implications of the uncertainties it has relied upon to justify a negative recommendation for remdesivir, including:

* it has not considered the range of probabilistic ICERs for remdesivir, which would have enabled it better to investigate the uncertainty associated with the various parameters e.g., by quantifying the percentage of simulations which fall below the cost-effectiveness threshold and presentation of confidence ellipses and scatter plots on the cost-effectiveness plane.
* it has not been able to consider a cost-effectiveness acceptability curve in the economic model, allowing visual inspection of the impact of uncertainty on the result in relation to different willingness to pay thresholds.
* it has not been able to consider the error probability that a treatment is not cost-effective.
* it has not been able to address the uncertainty from SOLIDARITY in the context of all relevant parameters.
* while accepting that “time to discharge” exerts an important influence on the cost-effectiveness estimates, the Committee has chosen not to investigate the uncertainty around this parameter and has therefore simply removed it.

With respect to equality issues, the Committee *noted the equalities issues outlined in section 3.24* [of the FDG] *and considered flexibility as part of the principles that guide the development of NICE guidance and standards….It noted that the issues raised could affect some people with protected characteristics disproportionately which would contribute to health inequality*. The Committee said that *in theory, it would be be willing to accept an ICER slightly more than what is usually acceptable if it addressed such health inequalities*. (FDG section 3.33).

However, by failing to conduct PSA, the Committee were unable to explore the impact of parameter uncertainty against the commonly accepted ICER thresholds and hence unable to consider how health inequalities may be addressed through the recommendation of remdesivir in specific subgroups.

Gilead raised concerns about the lack of probabilistic analysis in its response to the first EAG report (29 July 2022) and in its response to consultation on the DG (7 December 2022).

1(a).4 The Committee did not consider the cost-effectiveness for remdesivir for severe COVID-19 and so denied Gilead the opportunity to discuss commercial agreements that would mitigate or resolve the uncertainty around the ICERs

Committee approach

Generally, the Committee considered that the relative risks from early trials would lack generalisability (see Ground 2.1) and likely favour treatment compared with standard care because trials were done when hospitalisation and mortality were significantly higher. Therefore, the Committee considered that mean efficacy scenarios from these trials likely reflected the highest clinical effectiveness or “ceiling efficacy” of the treatment (FDG section 3.10).

The Committee concluded that *changes in best supportive care and higher vaccination rates mean that any limited relative treatment effects seen during the pandemic setting would have less effect in an endemic setting. This is because any limited benefit in the pandemic setting would likely be further limited or potentially have no difference in treatment effect compared with standard care (hazard ratios [HRs] would tend towards 1) in an endemic setting* (FDG section 3.12).

Applying this reasoning to the evidence provided by the updated NMA for remdesivir, the Committee noted *it was not possible to make a decision based on the confidence intervals of data from SOLIDARITY and the pooled NMA analysis* [(HR 0.85, 95% CI 0.76-0.95 for mortality versus standard care)] because *the precision around the confidence interval is reflective of population characteristics and standard care practices earlier on in the pandemic.* The Committee therefore *interpreted the available evidence with caution* *and considered a threshold analysis using the mortality rate ratios of 0.85 to 1.00* (FDG section 3.20).

The Committee *noted that any mortality benefit is likely to be minimal when the HRs are close to 1 and stronger clinical evidence is needed to justify a difference in relative clinical effects* and concluded that *there was insufficient evidence to show meaningful difference in mortality benefit with remdesivir versus standard care* in the severe COVID-19 setting (FDG section 3.20).

Based on this, the Committee concluded that it is not possible to reliably estimate remdesivir’s cost-effectiveness in treatment of severe COVID-19 requiring supplemental oxygen (FDG section 3.30). Consequently, the Committee did not present or consider any ICERs for remdesivir in this patient population.

This refusal to present or consider any ICERs is unfair and contrary to NICE’s published processes and methods

Section 3.1.1 of the Manual states that *[t]o ensure that the guidance issued by NICE is appropriate and robust, the evidence and analysis, and their interpretation, must be of the highest standard possible and transparent*. In order to meet this requirement in the context of this MTA, the Committee should have considered the best available evidence both of clinical efficacy and cost-effectiveness and should have addressed any identified uncertainty in the context of all the evidence presented. Instead, the Committee effectively ignored clinically significant results generated by large clinical trials such as SOLIDARITY and ACTT-1.

Applying a *ceiling effect* or *threshold* due to generalisability concerns is not appropriate as it does not appropriately capture the variation around the mean estimate. It is technically incorrect and procedurally unfair to rely only on the mean and upper confidence interval for decision making. Taking such an approach is a biased adjustment towards worse outcomes.

This approach is comparable to generating a tornado plot as part of one-way sensitivity analysis and then deciding to only look at one side of the plot, neglecting the other. Capturing sensitivity always requires taking both upper and lower confidence bounds into account alongside the mean estimate. Therefore, the Committee has failed to act fairly by not placing appropriate weight on high, mean, and low efficacy scenarios.

The Committee has not referred to any evidence in support of its application of a *ceiling effect* or *threshold*.

The Committee effectively relies on the same generalisability concerns both (i) to consider a threshold analysis and (ii) to believe that the mortality rate ratio would *tend towards 1* (FDG section 3.23). This is duplicative and so unfair: the Committee cannot rely on the same factors to justify both limbs of this approach.It also ignores the fact that large scale trials such as SOLIDARITY – including over 6,000 patients for the mortality analysis – are designed and powered to detect even minor benefits in treatment effect through the large sample size.[6]

In addition, the Committee has not provided reasons for the following inconsistencies in its approach:

* in the DG, when the Committee had less data on remdesivir, the Committee did consider cost-effectiveness and ICERs for remdesivir, albeit looking only at the low efficacy scenario. However, with the inclusion of additional evidence from SOLIDARITY, the Committee has concluded that it is unable to reliably estimate cost-effectiveness.
* the Committee took a different approach in respect of the PINETREE trial and assessed cost-effectiveness for remdesivir in mild COVID-19, despite acknowledging that *the PINETREE trial was conducted before the Delta wave and before the widely vaccinated and naturally immune population* (FDG section 3.13, pp.20). Both the SOLIDARITY and PINETREE trials were conducted during similar time periods (recruitment from early 2020 to early 2021), covered a range of similar geographical locations and PINETREE recruited only unvaccinated participants.

Impact

It is unfair to Gilead not to consider the ICERs for remdesivir. For severe COVID-19, ICERs developed by the EAG show that remdesivir is highly cost-effective for severe COVID-19, in the mean and high efficacy scenarios (without SOLIDARITY or ACTT-1) and that remdesivir is highly cost-effective across all efficacy scenarios (low, mean, and high) when considering SOLIDARITY and ACTT-1. (See EAG additional analysis post NICE Appraisal Consultation Document Table 4, page 14; Table 5, page 15 and paragraph 4.4.8, pp.31).

The Committee’s failure to consider cost-effectiveness has prevented Gilead from having the opportunity to discuss price and potentially resolve any outstanding uncertainty on cost-effectiveness.

See also Ground 1(a).10 regarding the assessment of time to discharge.

1(a).5 The Committee did not conduct a thorough assessment of treatments for children with severe COVID-19 and the resulting failure to recommend any treatment for children with severe COVID-19 is unfair and discriminatory

The Manual (paragraph 3.1.4) requires NICE to consider (amongst other factors) its *legal obligations on equality and human rights*, and *the requirement to treat people fairly*.

The Manual (paragraph 6.2.29) also requires the Committee to *consider carefully which individuals benefit most from the technology and whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost-effectiveness or cost savings.*

As set out below, these requirements have not been met in this appraisal.

Tocilizumab, the only product recommended in the FDG for severe COVID-19, is not licensed for children under 18 (FDG section 2.6). The Committee acknowledges that *by only recommending tocilizumab in the severe COVID-19 setting* *there is a risk of indirectly discriminating against children and young people.* *However, the alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources.* (FDG, section 3.32, pp.43).

Despite this acknowledgement, the Committee has not considered children with severe COVID-19 as a subgroup and has not given any reasons for failing to do so. This contrasts with the Committee’s approach to adults with high-risk of severe disease when nirmatrelvir plus ritonavir is contraindicated (FDG section 3.19).

The EAG explains that that *due to time constraints, the only sub-grouping considered was related to whether oxygen was required upon admission to hospital entry… The EAG is aware that other possible criteria for selecting subgroups include but are not limited to: age; immune system competence, comorbidities, seroprevalence; vaccination status and the predominant SARS-CoV-2 variant but did not have the time to explore the impact of these characteristics.* (EAG report v.3 3 October 2022, para 1.4.5 pp 25 – emphasis added). Yet again, the lack of time allocated to the MTA has adversely affected the outcome and is patently not a good reason for not addressing the clinical needs of a vulnerable group.

Remdesivir is the only COVID-19 treatment that is licensed in the UK for paediatric patients. In severe COVID-19, remdesivir is licensed for paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low-or high-flow oxygen or other non-invasive ventilation at start of treatment).

Even before this indication was licensed, remdesivir was demanded for use in children with severe COVID-19 under an early access scheme. Since the onset of the pandemic, Gilead has approved remdesivir for paediatric compassionate use for 263 patients under the age of 12 years, and 22 patients over the age of 12. While small numbers, the current FDG does not address the needs of this vulnerable and protected characteristic cohort.

As highlighted by the British Paediatric Allergy Infection and Immunity Group (BPAIIG) in its response to consultation on the DG: *Reassuring safety and pK data is available from well-designed clinical trials for remdesivir in those under 18 years of age. In addition, carefully reported observational data is also available*… *Furthermore, the disease phenotype in younger children is more of an acute viral syndrome (similar to other acute viral respiratory infections) rather than the hyperinflammatory process observed in older age groups. Efficacious antiviral agents are therefore likely to play more of a role than anti-inflammatory agents in this age range*… *These considerations do not appear to have been adequately discussed or taken in to account when making this recommendation which could be considered discriminatory against this age group.*

Gilead also raised its concerns about the lack of treatment for children with severe COVID-19 in its response to consultation on the DG.

The Committee’s appraisal of remdesivir engages Articles 2 (the right to life), 8 (the right to private and family life) and 14 (the right not to be discriminated against) of the European Convention on Human Rights (ECHR) and these factors must be considered by the Committee when making its decisions. Age is a protected characteristic under the Equality Act 2010 and public authorities have a duty to consider how their decisions affect people who are protected under the Act. Before making a decision that no treatment should be recommended for severely ill children (although treatments are recommended for all other individuals), the Committee is required to consider the position of the excluded group in the specific context of their status as children. However, the Committee has not recommended any treatment for children with severe COVID-19 and, in making that decision, it has not carried out a thorough assessment of the only licensed treatment, including a well-informed assessment of cost-effectiveness for this discrete group or otherwise considered the status of children with severe COVID-19 in the context of its public sector equalities duties.

The Committee is required to ask itself whether the approach should change to reflect the fact that the population excluded from treatment are children and give a reasoned answer. In support of this submission, Gilead refers to the decision of the NICE Appeal Panel who considered the appeal against the draft final guidance for dinutuximab for treating high-risk neuroblastoma.

1(a).6 The Committee has not given any adequate reasons for not addressing the distinction between patients with severe COVID-19 on low-flow oxygen and those on high-flow oxygen despite this clear distinction being made in current guidance

Section 6.2.29 of the Manual requires the Committee to *consider carefully which individuals benefit most from the technology and whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost-effectiveness or cost savings.*

The Committee recognises the distinction made in current guidance between patients with severe COVID-19 on low-flow oxygen and those on high-flow oxygen (FDG section 3.9). However, the Committee apparently dismisses this distinction by stating that *clinical experts considered that remdesivir is currently used in some people with lower oxygen needs but its use is not clearly defined*. (FDG section 3.2).

This is not a real or adequate reason for not reflecting this distinction in the Committee’s recommendations because:

the use of remdesivir in low-flow settings is clearly defined, by a robust evidence base. The distinction between patients requiring low-flow or high-flow oxygen is reflected in the marketing authorisation for remdesivir (SmPC section 5.1, Table 7).

what constitutes low-flow oxygen is also clearly defined: NICE’s own COVID-19 rapid guideline defines low-flow supplemental oxygen as oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.[7] This reflects the general understanding of low-flow oxygen, as clarified in Gilead’s ACTT-4 study.[8, 9]

evidence-based guidelines clearly recommend remdesivir in those requiring low-flow oxygen, including the NHSE Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised due to COVID-19 and NICE’s own COVID-19 rapid guideline: managing COVID-19, as well as ESCMID COVID-19 Living Guidelines and NIH COVID-19 Treatment Guidelines.[1-3, 7, 10]

The subgroup of patients requiring low-flow oxygen is therefore a distinct and readily defined population.

Impact

By failing to distinguish between low-flow and high-flow oxygen, the Committee has, contrary to the Manual’s requirements, failed to consider a subgroup of patients with severe COVID-19 who would benefit most from remdesivir, and for whom remdesivir would be a clinically and cost-effective treatment. This subgroup would include vulnerable groups for whom there may not be an alternative antiviral treatment or any treatment available (see Grounds 1(a).5 and 2.2).

A consistent mortality benefit has been demonstrated with remdesivir use in those requiring low oxygen support in ACTT-1, the final SOLIDARITY results and a plethora of real-world datasets, as referenced in Gilead’s prior submissions.

Gilead raised its concerns on this issue in its response to the first EAG report, in its targeted evidence submission and in its response to consultation on the DG.

1(a).7 Gilead was not given a fair hearing because it was not given the opportunity to discuss key issues at the appraisal committee meetings.

Gilead was not given an adequate hearing at the appraisal committee meetings (**ACMs**), contrary to principles of fair process and also section 5.5.6 of the Manual, which reflects NICE’s *aim to make sure that companies bringing technologies forward for possible use in the NHS can make the best plausible case for its product, to the ultimate benefit of the NHS and patients*.

Gilead raised its concerns about the conduct of the first ACM in its response to consultation on the DG.

In the first ACM (18 October 2022), each company was only given the opportunity to answer one question, despite the complexity of the topic, attendant uncertainties, the number of products involved and clear contention over some of the assumptions. In the briefing to companies immediately before the meeting, the Chair emphasised that he was primarily interested in hearing from Committee members and not companies and deterred companies from contributing, warning them against requesting to speak on the virtual call as this would make him very unhappy.

In the second ACM (24 January 2023), key issues were not raised or addressed:

In the DG issued for consultation, the Committee stated that the inclusion of SOLIDARITY *would have likely impacted the final conclusions for remdesivir* (DG section 3.12).

Inclusion of SOLIDARITY was one of four key issues flagged in this second meeting by the Chair, but no time was allowed for this discussion. In particular, Gilead was not given the opportunity to discuss real-world evidence demonstrating maintained efficacy of remdesivir against the Omicron variant. By contrast, time was dedicated to discussion on real-world evidence relating to sotrovimab.

During this meeting, Gilead only had the opportunity to ask if SOLIDARITY data would be included, to which the Committee Chair replied that SOLIDARITY data was “*firmly in*.” This response was potentially misleading: Gilead was not told, and so was not given the opportunity to discuss, the main reason why the Committee ultimately did not recommend remdesivir - namely the Committee’s conclusion that, despite the inclusion of SOLIDARITY in the EAG model, the Committee considered that, in view of generalisability concerns it was not possible to reliably estimate remdesivir’s cost-effectiveness in treatment of severe COVID-19. This meant that Gilead was not given an opportunity to raise important questions about the Committee’s approach (see Grounds 1(a).4 and 2.1).

1(a).8 NICE treated Gilead unfairly compared to another stakeholder company by refusing to consider new data that could potentially change the Committee’s final conclusions

On 31st January 2023, NICE informed all stakeholders that certain products, including sotrovimab (Xevudy), would not be recommended for treating COVID-19.

On the same day, NICE briefed Gilead on the Committee’s conclusions after the second meeting. Given the impression given in the second ACM (see above), this was the first time that Gilead heard how the Committee’s concerns about generalisability of SOLIDARITY would result in remdesivir not being recommended for severe COVID-19.

In response, on 9 February 2023 Gilead asked for an additional ACM, highlighting the lack of debate about the generalisability of remdesivir trials. The following day, Gilead provided additional data to NICE that addressed the generalisability of SOLIDARITY, to support its request for a third ACM.

The submitted evidence (which recently become available after the second ACM) included a study to be presented at the Conference on Retroviruses and Opportunistic Infections (**CROI**).[11] This study leveraged data from the Premier Healthcare Database up until the Omicron phase (December 2021 – April 2022), analysing more than 200,000 patients. Data from this study clearly demonstrates that remdesivir reduces mortality in hospitalised COVID-19 patients across all variant eras, including the Omicron phase. In particular, Gilead presented an updated NMA for all hospitalised patients treated with remdesivir, which showed that the mean mortality benefit of remdesivir treatment was a risk ratio of 0.82 [95% CI: 0.79-0.85] using a fixed effect model.[12] As demonstrated by these results, even the upper confidence interval is significantly below 1, indicating an unambiguous mortality benefit for remdesivir in the hospital setting. Furthermore, this analysis is extremely robust, as it compared over 30,000 remdesivir patients with over 27,000 non-remdesivir patients, summarising results of 10 independent studies.

The updated NMA would address a number of key concerns outlined in the FDG: for example, by demonstrating significant reductions in mortality, it would reduce the uncertainty over the size of the mortality benefit of remdesivir, and the generalisability of SOLIDARITY.

However, NICE refused Gilead’s request for a further ACM.

On 13th February 2023, NICE informed stakeholders that, contrary to NICE’s communication on 31st January 2023, sotrovimab would be recommended in people at high-risk of progressing to severe COVID-19, if nirmatrelvir/ritonavir is contraindicated or unsuitable.

In NICE’s press release for its FDG, NICE explains that *following the consideration of more clinical evidence and productive discussions with the company,* [NICE is] *now able to recommend Xevudy as a cost-effective option.*

From these statements, it appears that NICE took account of more clinical evidence, submitted after 31st January 2023, in order to change its recommendation regarding sotrovimab. No reason has been provided to justify the unequal treatment of Gilead compared to GlaxoSmithKline. In view of the potential for the new remdesivir evidence to change the Committee’s conclusions, such inequality is unfair.

1(a).9 The Committee has not given adequate reasons why differences in standard care give rise to significant concerns about the generalisability of SOLIDARITY data

Committee approach

In its discussion on remdesivir (FDG section 3.20), the Committee noted that *it was not possible to make a decision based on the confidence intervals of data from SOLIDARITY and the pooled NMA analysis… because the precision around the confidence interval is reflective of population characteristics and standard care practices earlier on in the pandemic*. This contributed to the Committee’s conclusion that it could not reliably estimate cost-effectiveness for remdesivir (see Ground 1(a).4).

For SOLIDARITY, the Committee noted (FDG section 3.13) *key study limitations highlighted in the trial publication, including that standard care differed within and across countries*. The Committee understood that *standard care including dexamethasone use* *and hospital practices of escalation to mechanical ventilation as part of standard care, varied in hospitals when SOLIDARITY was done*. The Committee contrasted this with the standard care in trials for tocilizumab, *which included multiple UK sites*, was *reflective of standard care in NHS clinical practice* *and was considered* *be more generalisable to the endemic setting than the SOLIDARITY standard care*.

These are not adequate reasons for concluding that there are significant generalisability concerns for SOLIDARITY data

The Committee’s position is in stark contrast to the assessment of heterogeneity by the authors of the SOLIDARITY trial, who concluded that “*heterogeneity between the collaborating countries and hospitals does not bias the comparison of study drug versus control, as all could give the allocated treatment and report the study outcomes reliably*”.

The Committee has not explained:

* what it considers to be the differences in standard care between the UK and the other countries covered by SOLIDARITY (at the time that trial was conducted or more recently) why these differences negate the fact that remdesivir use resulted in a mortality benefit against the range of standard care provided. For example, the SOLIDARITY results show that there was little difference between treatment groups in use of corticosteroids (2782 [67·1%] of 4146 for remdesivir vs 2820 [68·3%] of 4129 for control), IL-6 inhibitors, or other non-study drugs. Ventilation was more resource-limited in some countries or hospitals than others, and some patients who were not ventilated would have been ventilated had resources been available. This situation does not, however, invalidate the secondary analyses of ventilation or the composite outcome of death or ventilation (which is unaffected by any deaths that could have been prevented by ventilation).

1(a).10 The Committee’s exclusion of treatment effects for hospital time to discharge data for remdesivir is unfair because these treatment effects were reflected in the base-case ICER results for tocilizumab.

In its assessment, the EAG included hazard ratio of time to discharge (**TTD**) in the clinical endpoints considered for the severe COVID-19 setting. (FDG section 3.10).

During consultation on the DG, Gilead highlighted that the TTD data from ACTT-1 should have been included for remdesivir and provided evidence on TTD for remdesivir.

In response to consultation on the DG, the EAG included the TTD data for remdesivir only as a sensitivity analysis and not as part of a new base-case for the Committee’s consideration. By contrast, from the first EAG Report of 30 June 2022 (Table 4, pp 26), TTD data for tocilizumab was incorporated into the base-case for this product, as it was reflected in the metaEvidence initiative results.

In the FDG, the Committee acknowledged that *the EAG included the time to discharge data for remdesivir* *which* *resulted in a large reduction in the cost-effectiveness estimates*. (FDG section 3.23).

However, the Committee explained that it *was uncertain about the treatment benefit* [regarding TTD] *in an endemic setting* and *concluded that it was reasonable to remove these treatment effects*. (FDG section 3.23). Consequently, the Committee did not further consider the impact of TTD data in cost-effectiveness estimates for remdesivir.

Despite this stated conclusion, the base-case ICER results for tocilizumab compared to standard of care presented in the updated EAG report (3 October 2022, Table 4 pp 30) and in the EAG additional analysis post NICE Appraisal Consultation Document (13 January 2023; Table 1, pp 4) still include the TTD data for tocilizumab, and positively favour NICE’s recommendation of tocilizumab. Likewise, the TTD data for tocilizumab is reflected in the latest version of the EAG’s economic model (v5.1, dated 17th November 2022).

Although the Committee states that the EAG *included scenarios that removed treatment effects on time to discharge and clinical improvement at 28 days to try to account for these potential uncertainties* (FDG section 3.23), these scenarios do not appear to have been published and so Gilead cannot assess their impact.

It is unfair to adversely discriminate against Gilead (compared to Roche) by disregarding the ACTT-1 data on TTD for remdesivir, including in the base-case results, especially in view of the large reduction in cost-effectiveness estimates resulting from the inclusion of the ACTT-1 data.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 The Committee’s conclusion that significant uncertainty remains in terms of generalisability of the trial evidence for remdesivir in severe COVID-19 is unreasonable because it ignores clinical practice and in-vitro data that has not been countered

The Committee (FDG section 3.12) acknowledged that most trials informing clinical efficacy (across all products considered in the appraisal) pre-dated the Omicron variant and highlighted the main generalisability concerns to be:

* changes in population immunity through natural immunity and vaccination.
* changes in the pathogenicity of the virus.
* increased effectiveness of supportive care.
* other differences that were specific to the context of a pandemic setting.

The Committee considered that the relative risks from these trials would lack generalisability because there would be interaction between some of these concerns and treatment effect in the trial, likely favouring treatment compared with standard care because trials were done when hospitalisation and mortality were significantly higher (FDG section 3.12).

Applying this to remdesivir, the Committee concluded that SOLIDARITY was an early study in the pandemic and there was *no clinical evidence available for remdesivir in the context of the current endemic setting* *with a widely vaccinated and naturally immune population and the Omicron variant. Therefore, significant uncertainty remained in terms of generalisability of the trial evidence for remdesivir*. (FDG section 3.13).

This approach is unreasonable for the following reasons:

Changes in population immunity through natural immunity and vaccination

Using the natural immunity or vaccination status of patients to justify lack of generalisability ignores clinical practice: if a patient is hospitalised with severe COVID-19, the treatment required, and its efficacy, is largely unaffected by their vaccination status. In this situation, the individual’s immune protection (either though vaccine or natural immunity) has not been effective in preventing severe disease, for example because the patient is immune-supressed. The absence of clear data that vaccination equalises risk of severe disease in those at high-risk of disease progression is well described in the McInnes report.[13]

The Committee itself acknowledged the explanation from the clinical experts that *people presenting in hospital with COVID-19 are mainly either unvaccinated or immunocompromised or did not have an immune response to vaccines* (section 3.3).

Changes in the pathogenicity of the virus

The Committee’s conclusion ignores the in-vitro data and real-world evidence submitted by Gilead in response to consultation on the DG (7.3.2, 7.3.3) and reflected in the marketing authorisation for remdesivir (Part 5.1, Table 6 of the SmPC).

Gilead submitted evidence (in its response to consultation on the DG) that remdesivir retains antiviral potency against all known clinical isolates of all known SARS-CoV-2 variants in-vitro, including Alpha, Beta, Gamma, Delta, Epsilon, Zeta, Iota, Kappa, Lambda, and Omicron.

The Committee’s conclusions disregard the in-vitro evidence considered by the Committee, and from which the Committee concluded that there was *no in-vitro evidence showing reduced clinical efficacy of the antivirals (… remdesivir) … across the variants tested* (FDG section 3.16).

The Committee explains that it was *cautious* about the treatment effect of remdesivir shown in this observational evidence because the original SOLIDARITY evidence already showed limited mortality benefit (FDG section 3.13 pp 21) but gives no reason for ignoring the in-vitro data, in particular in combination with the observational data.

The Committee has not referred to any evidence that remdesivir is less effective against Omicron or other variants of concern, to counter the above evidence.

Gilead notes that the authors of SOLIDARITY also addressed the fact that trial recruitment preceded the Omicron variant and widespread vaccination but explained that *for drugs such as remdesivir that act via internal non-structural proteins (NSPs), the emergence of these new viral variants might not materially affect drug efficacy*.

Increased effectiveness of supportive care / Standard of Care

See Ground 1(a).9 above.

Other differences that were specific to the context of a pandemic setting

Although the Committee referred to these differences, it provided no explanation or examples of such differences.

2.2 The Committee’s recommendations are unreasonable because, ignoring clinical need and practice, they fail to recommend any antiviral treatment for patients with severe COVID-19

Under the FDG, only tocilizumab (an anti-inflammatory) would be recommended for patients with severe COVID-19.

This outcome ignores the important role of antivirals for these patients in clinical practice in particular in earlier stages of severe disease and results from the Committee unreasonably treating antivirals and immunomodulators as mutually exclusive.

Clinical need

Patients with severe COVID-19 can have prolonged active viral replication (up to 4 weeks after symptom onset, as demonstrated by cytopathic effects) and therefore require an antiviral intervention.[14] Given that viral replication is a key driving factor for the systemic inflammatory response among these patients, the antiviral mechanism of action of remdesivir is a critical component of the multifaceted care of patients with severe disease.

This applies in particular to immunocompromised patients who are less likely to be able to mount an immune response to clear the virus, and a large proportion may also have contraindications to Paxlovid use e.g., DDIs with chemo agents, renal and liver disease: as noted in Gilead’s response to consultation on the DG (section 8.2). Paxlovid which has been found to have high contraindications (up to 15% of patients as reported by Lim *et al.,* (2022) and >37% for patients with comorbidities and 27% in older patients according to Hoertel *et al.,* (2022).[15, 16] This vulnerable group, at high-risk of further disease progression, would have, under the FDG, no access to antivirals to reduce the viral burden that will drive the hyperinflammatory response.

In their response to consultation on the DG, the Royal College of Physicians raised concerns that the FDG would provide anti-inflammatory therapy only for hospitalised patients requiring oxygen, with no antiviral or neutralising mAB provision. The Royal College of Physicians emphasised that *there is a transition period, even in those with more severe disease, who have both ongoing viral replication and a growing inflammatory response. There is likely a role for both antiviral and anti-inflammatory treatment in this patient group*.

For those with ongoing viral replication (particularly the highest risk immunocompromised patients), the ongoing viraemia will be driving the hyper-immune response.

Antivirals and immunomodulators are not mutually exclusive

In the FDG, the Committee presents treatment with antivirals as mutually exclusive to treatment with immunomodulators (tocilizumab) for severe COVID-19.

This ignores:

* comments made by clinical experts to the Committee (FDG section 3.9) that, in practice, *for people hospitalised with severe COVID-19, anti-inflammatories are used along with antivirals and neutralising monoclonal antibodies, based on the NHS interim clinical commissioning policies for secondary care… The clinical experts said a hierarchical flow of treatments is followed in the hospital and recommending one treatment over another is challenging*.
* data on use of remdesivir in combination with tocilizumab - see Gilead’s response to consultation on the DG section 7.2.2, second bullet).
* international, evidence-based guidelines that recommend combination therapies.[2-4, 7, 17]

## Conclusion

Gilead requests that this appeal should be determined at an oral hearing.

As a result of this appeal, the appeal panel is respectfully requested to return this appraisal for further consideration by the Committee, including with the following directions:

Conduct a separate appraisal on the use of remdesivir in the treatment of severe COVID-19, allowing Gilead to provide an economic model and other evidence, and generally to participate in accordance with NICE published processes and methods.

In any separate appraisal, or in any event in this MTA,

* address as subgroups (i) patients on low-flow oxygen and (ii) children.
* re-consider the generalisability of the SOLIDARITY trial on mortality benefit and represent ICERs including this data.
* consider additional evidence presented by Gilead (sent to NICE on the 10th of February 2023) on the effectiveness of remdesivir in severe COVID-19 to ensure that the final decision is up to date, including CROI 2023; Lancet pre-print publication (Amstutz *et al.,* 2023) and Gilead NMA (submitted to Health Sciences Review journal).[11, 12, 18]
* consider results from a PSA on the EAG model, including SOLIDARITY and ACTT-1 data on mortality and TTD in the base-case, and consider resulting probabilistic ICERs and cost-effectiveness acceptability curves.
* if ICERs considered are close to the cost-effectiveness threshold either generally or for any subgroup, provide Gilead with the opportunity to engage in commercial discussions.

We thank you in advance for considering Gilead’s submissions in this appeal. We are available to answer any questions you may have or provide further clarifications.

Yours sincerely,

xxxxxxxxxxxx Executive Director, Gilead Sciences Ltd

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