



**Health  
Information  
and Quality  
Authority**

An tÚdarás Um Fhaisnéis  
agus Cáilíocht Sláinte

## **Advice to the National Public Health Emergency Team:**

# **Interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19**

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## About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

## Foreword

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious virus, which has caused nearly 100 million cases of COVID-19 since its emergence in 2019, with a considerable level of associated mortality. In the context of the ongoing COVID-19 pandemic, SARS-CoV-2 constitutes a significant public health concern due to its high basic reproduction rate, the absence of innate immunity in the human population, the limited evidence of effective treatment approaches, and the constrained supply of vaccines in the early stages of population-level immunisation programmes.

The National Public Health Emergency Team (NPHE) oversees and provides national direction, guidance, support and expert advice on the development and implementation of strategies to contain COVID-19 in Ireland. Since March 2020, HIQA's COVID-19 Evidence Synthesis Team has provided research evidence to support the work of NPHE and associated groups and inform the development of national public health guidance. The COVID-19 Evidence Synthesis Team, which is drawn from the Health Technology Assessment Directorate in HIQA, conducts evidence synthesis incorporating the scientific literature, international public health recommendations and existing data sources, as appropriate.

From September 2020, as part of the move towards a sustainable response to the public health emergency, HIQA provides evidence-based advice in response to requests from NPHE. The advice provided to NPHE is informed by research evidence developed by HIQA's COVID-19 Evidence Synthesis Team and with expert input from HIQA's COVID-19 Expert Advisory Group (EAG). Topics for consideration are outlined and prioritised by NPHE. This process helps to ensure rapid access to the best available evidence relevant to the SARS-CoV-2 outbreak to inform decision-making at each stage of the pandemic.

The purpose of this report is to outline the advice provided by HIQA to NPHE regarding the evidence for interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19.

HIQA would like to thank its COVID-19 Evidence Synthesis Team, the members of the COVID-19 EAG and all who contributed to the preparation of this report.



**Dr Máirín Ryan**

Deputy CEO & Director of Health Technology Assessment

Health Information and Quality Authority

## Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this work.

Particular thanks are due to the COVID-19 Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice and information.

Membership of the Expert Advisory Group involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to NPHE. It does not necessarily imply agreement with all aspects of the evidence synthesis or the subsequent advice.

### The membership of the EAG was as follows:

<b>Prof Karina Butler</b>	Consultant Paediatrician and Infectious Diseases Specialist, Children's Health Ireland & Chair of the National Immunisation Advisory Committee
<b>Dr Jeff Connell</b>	Assistant Director, UCD National Virus Reference Laboratory, University College Dublin
<b>Dr Eibhlín Connolly</b>	Deputy Chief Medical Officer, Department of Health
<b>Prof Máire Connolly</b>	Specialist Public Health Adviser, Department of Health & Professor of Global Health and Development, National University of Ireland, Galway
<b>Prof Martin Cormican</b>	Consultant Microbiologist & National Clinical Lead, HSE Antimicrobial Resistance and Infection Control Team
<b>Ms Sinead Creagh</b>	Laboratory Manager, Cork University Hospital & Academy of Clinical Science and Laboratory Medicine
<b>Dr Ellen Crushell*</b>	Consultant Paediatrician, Dean, Faculty of Paediatrics, Royal College of Physicians of Ireland & Co-Clinical Lead, Paediatric/Neonatology National Clinical Programme
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<b>Mr Andrew Lynch</b>	Business Manager, Office of the National Clinical Advisor and Group Lead - Mental Health, HSE
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<b>Dr John Murphy*</b>	Consultant Paediatrician & Co-Clinical Lead, Paediatric/Neonatology National Clinical Programme, HSE
<b>Dr Sarah M. O'Brien</b>	Specialist in Public Health Medicine, Office of National Clinical Advisor & Group Lead (NCAGL) for Chronic Disease
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<b>Dr Michael Power</b>	Consultant Intensivist, Beaumont Hospital & Clinical Lead, National Clinical Programme for Critical Care, HSE
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\* Alternate nominee for programme and or association

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### **Members of HIQA's COVID-19 Evidence Synthesis Team:**

Susan Ahern, Natasha Broderick, Paula Byrne, Karen Cardwell, Paul Carty, Barbara Clyne, Laura Comber, Christopher Fawsitt, Patricia Harrington, Karen Jordan, Kirsty O'Brien, Eamon O Murchu, Michelle O'Neill, Sinead O'Neill, Máirín Ryan, Debra Spillane, Susan Spillane, Conor Teljeur, Barrie Tyner, Kieran Walsh.

The advice is developed by HIQA's COVID-19 Evidence Synthesis Team with support from HIQA's COVID-19 Expert Advisory Group. Not all members of the Expert Advisory Group and Evidence Synthesis Team are involved in the response to each research question. The findings set out in the advice represent the interpretation by HIQA of the available evidence and do not necessarily reflect the opinion of all members of the Expert Advisory Group.

### **Conflicts of Interest**

None declared.

## **Advice to the National Public Health Advisory Team**

The purpose of this report is to provide advice to the National Public Health Emergency Team (NPHE) on the following policy question:

"What is the emerging evidence in relation to (i) pharmaceutical and (ii) lifestyle interventions post diagnosis of COVID-19 in the community aimed at minimising progression to severe disease?"

The response to the policy question was informed by an evidence synthesis considering two elements:

1. Evidence for the effectiveness of (i) pharmaceutical and (ii) non-pharmaceutical interventions, in the community setting, aimed at reducing progression to severe disease in individuals with confirmed or suspected COVID-19
2. Input from the COVID-19 Expert Advisory Group.

### **Evidence for the effectiveness of interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19**

The key points of this evidence synthesis, which informed HIQA's advice, are as follows:

- A rapid evidence review was conducted to identify studies on the effectiveness of (i) pharmaceutical and (ii) non-pharmaceutical interventions, in the ambulatory setting, aimed at reducing progression to severe disease in individuals with confirmed or suspected COVID-19.
- For the purpose of this evidence summary, only controlled trials with published effectiveness data were included. The following studies of interventions were excluded:
  - ongoing trials without published interim or preliminary results
  - trials that enrolled patients from both inpatient and ambulatory settings, but did not report disaggregated data relating to the ambulatory group
  - trials that included interventions against which regulatory agencies (such as the EMA, FDA, MHRA) have issued warnings on the basis of potential harms (such as hydroxychloroquine).
- No trials were identified relating to non-pharmaceutical interventions (lifestyle, physiotherapy, respiratory therapy, psychological therapy, organisational or technological interventions).

- Eight randomised controlled trials (RCTs) were identified relating to nine pharmaceutical interventions. Seven of these trials enrolled adults  $\geq 18$  years with one trial enrolling adults and adolescents  $\geq 16$  years. At the time of enrolment, all patients had RT-PCR confirmed COVID-19 and were not hospitalised. The median number of participants in trials was 198 (range: 62-577) with a median duration of follow-up of 25 days (range: 5-29).
- None of the nine interventions identified are currently authorised for the treatment of COVID-19 by the European Medicines Agency (EMA); five of the nine interventions are not authorised for any indication by the EMA (casirivimab plus imdevimab, bamlanivimab, bamlanivimab plus etesevimab, nitazoxanide, sulodexide).
- 'Low certainty' evidence in support of potential effectiveness was found for two interventions: fluvoxamine versus placebo to prevent clinical deterioration, and the combination monoclonal antibody treatment bamlanivimab plus etesevimab versus placebo to prevent hospitalisation or emergency department visits. However, both trials were limited by small sample sizes and short durations of follow-up; the results should therefore be considered exploratory in nature. The determination of clinical efficacy and safety will require larger, robust RCTs to be conducted.
  - In one preliminary RCT, patients who received fluvoxamine had a lower risk of clinical deterioration than patients who received placebo (absolute risk difference 8.7% [95% CI: 1.8%-16.4%]; low certainty evidence; 152 participants were followed for 15 days).
  - In one RCT, patients who received the combination monoclonal antibody therapy bamlanivimab plus etesevimab were observed to have a reduced risk of hospitalisations or emergency department visits compared with patients who received placebo (absolute difference 4.9% [95% CI: 0.8%-8.9%]; low certainty evidence; 268 participants were followed for 29 days). No significant difference versus placebo was observed for patients who received bamlanivimab as monotherapy (at any dose, 700mg, 2800mg or 7000mg) , for this outcome.
- 'Very low certainty' evidence was identified from a further two studies (both published as preprints) of two interventions: ivermectin plus doxycycline and sulodexide. Serious concerns were raised with regard to the high risk of bias, small sample sizes and short durations of follow-up within the trials. As such, results from these studies should not be used to inform decision-making with

respect to effectiveness. Neither study was considered applicable to the Irish healthcare setting due to differences in usual care provided in the trials.

- No statistically significant difference in the rates of clinical deterioration or hospitalisation was reported for the following interventions, compared with placebo or usual care in the outpatient setting: bamlanivimab (as monotherapy), casirivimab plus imdevimab (at interim analysis of one RCT), ivermectin (as monotherapy), nitazoxanide and peginterferon lambda. Additionally, there were concerns identified in relation to the risk of bias, small sample sizes and short durations of follow-up within a number of these trials. The ivermectin and nitazoxanide trials were considered not applicable to the Irish healthcare setting due to differences in usual care provided in the trials.
- Given the lack of regulatory authorisation of any of the interventions for the treatment of COVID-19 in the ambulatory setting, no robust assessment of safety has been performed to date with respect to their use for this indication. Furthermore, the results presented within the trials herein described are insufficient for establishing the safety profile of the interventions; this is a consequence of small sample sizes, short duration of follow-up, and insufficient assessment and reporting of safety outcomes across the trials.
- In conclusion, there is currently insufficient evidence of either effectiveness or safety to support the use of any pharmaceutical intervention in the community setting to reduce the risk of progression to severe disease in patients who have been diagnosed with COVID-19, unless as part of an ongoing monitored clinical trial. Furthermore, no evidence was identified for the effectiveness or safety of any non-pharmaceutical intervention in the community setting.

### **COVID-19 Expert Advisory Group**

- A meeting of the COVID-19 Expert Advisory Group (EAG) was convened for clinical and technical interpretation of the evidence provided.
- The EAG agreed that evidence regarding the effectiveness of therapeutic interventions, particularly for pharmaceutical treatments, must be subject to the highest standards of rigour. It was noted that trials included in the present review are severely limited with respect to the certainty, quantity, and applicability of the evidence and are insufficient to inform decision-making on treatment options for COVID-19 in Ireland.
- The EAG agreed that there is currently no evidence of benefit associated with the treatments considered within the present review and there is insufficient information on whether any of these may be safely used in the treatment of

COVID-19. Furthermore, some of the interventions investigated within the trials would not be considered applicable to the Irish setting due to differences in the standard of care and or on the basis of safety concerns.

- It was noted that to be recommended as a treatment for patients with mild to moderate COVID-19 in the community setting, such treatment would have to adhere to the usual requirements for robust clinical governance with strong evidence of effectiveness and safety.
- A distinction was drawn between interventions for which there is no evidence in any setting versus those for which there is evidence in another setting (for example, acute care). Evidence in relation to the potential to cause harm should include trial data, but should be supported by the broader literature with respect to that intervention.
- In consideration of the fact that evidence exists in support of the use of corticosteroids to treat hospitalised patients with severe COVID-19, it was noted that no evidence was identified for the use of corticosteroids to treat COVID-19 in the community. While there are anecdotal reports of corticosteroids being used in the community, it was highlighted that evidence of benefit for dexamethasone in the RECOVERY clinical trial was limited to patients with severe disease who required supplemental oxygen. Moreover, there was evidence that dexamethasone might increase mortality in hospitalised patients who do not require supplemental oxygen.
- While none of the pharmaceutical interventions identified in the review are currently licensed for the treatment of COVID-19, it was noted that Schedule 1 of the Medicinal Products Regulations 2007 includes an [exemption](#) for practitioners to prescribe unauthorised medicinal products for individual patients under their direct responsibility, in order to fulfil the special needs of those patients.
- It was noted that where treatments outlined in the identified trials may technically be acquired for off-label use on an individual patient basis, the doses used within some of the trials represent higher doses than those routinely used in clinical practice, thus raising further safety concerns.
- It was suggested that general practitioners should receive very clear communication that, based on the current evidence, there are no medicines that should be prescribed outside of a clinical trial for the treatment of COVID-19 in the community. Opportunities for communication include GP webinars and other settings presented by the Irish College of General Practitioners (ICGP). Such communication, when supported by a comprehensive evidence review such as the one that has been undertaken, will help ensure that:
  - individuals do not prescribe or use interventions for the treatment of COVID-19 that do not meet the necessary minimum criteria

- practitioners are not criticised for not prescribing these interventions.
- It was noted that the HSE has established ongoing processes for development of clinical guidance with respect to SARS-CoV-2 infection. This includes guidance for the clinical management of COVID-19 in the acute setting, which is approved for use by the HSE National Clinical Advisor and Group Lead, Acute Hospitals Division. The published guidance is developed by guideline review groups and informed by rapid evidence reviews undertaken by the HSE COVID-19 Evidence Review Group for Medicines. This latter group comprises evidence synthesis practitioners from the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The HSE COVID-19 Evidence Review Group has also published evidence summaries in relation to specific interventions for both ambulatory and hospital use. These processes are linked with established medicines management and purchasing schemes. While the HIQA review provides information on emerging evidence, it does not supersede the ongoing processes for guidance development and or the reimbursement of medicines as described.
- If evidence of effectiveness should emerge in the future, the following were noted as important factors that would need to be considered:
  - Due process would apply in decision-making regarding the recommendation of a treatment and the reimbursement of any medicine that may be recommended.
  - There is currently very poor infrastructure in place for the delivery of infusions in the community generally, with significant additional challenges regarding the delivery of infusions for patients with COVID-19. Due to this, there are significant concerns regarding availability of resources and feasibility of implementation.
  - With respect to monoclonal antibody treatments, it was noted that SARS-CoV-2 variant resistance may occur; as such, effectiveness evidence may be specific to time and place and may not apply universally as the pandemic evolves.
- The high standard of evidence required for pharmaceutical interventions, particularly in the context of population-level recommendations, was reiterated. Demonstration of a clinically relevant estimate of effect should be required prior to medicine being adopted for use. Concerns were raised about the pre-prints, that is, manuscript publications which have yet to be formally peer-reviewed, included in the review. It was noted that for some agents, this was the only evidence available, emphasising the lack of robust evidence currently available to inform decision-making.
- It was acknowledged, that conducting controlled clinical trials in the primary care setting during the pandemic is challenging, and as such there may continue to be

a lack of robust evidence to inform decision making. This was viewed as particularly relevant to the generation of evidence on non-pharmaceutical interventions.

- It was highlighted that there has been widespread discussion in the media, and among clinicians, regarding the potential use of certain interventions for the treatment of COVID-19 in the community; for instance Vitamin D, corticosteroids, and the use of pulse oximetry by patients. It was agreed that the advice pertains to medicines explicitly for the treatment of COVID-19 and does not pertain to the routine use of these medicines for other indications (for example, use of corticosteroids in patients with an exacerbation of COPD or asthma).
- It was recognised that, as with pharmaceutical interventions, there may be harms associated with non-pharmaceutical interventions. For example, the widespread use of pulse oximetry by patients, in the absence of clinical supervision, may lead to delayed presentation by patients who have been falsely assured by readings that have been incorrectly taken or taken using devices that have not been validated. Alternatively this intervention could contribute to anxiety and additional emergency department attendances in others where their baseline clinical context has not been taken into consideration. It was noted that remote pulse oximetry monitoring of COVID-19 patients in the community has been deployed by at least one hospital, but that this is in the context of validated devices for which there is centralised monitoring and ongoing clinical oversight.
- It was noted that once a medical device has been CE marked (this indicates that a product conforms with health, safety, and environmental protection standards within the European Economic Area), there is no legal impediment to it being placed on the market. However, there are risks with this interpretation as it does not mean that safety and efficacy have been demonstrated.
- The potential role of HSE Community Assessment Hubs was noted. While the evidence review did not identify international literature with respect to such hubs, it was noted that they play an important role in Ireland in terms of patient triage. This can help ensure that those requiring hospital review are promptly referred, while providing assurance to other patients, including very anxious patients, that their needs can adequately be met in primary care without ED attendance.
- It was noted that evidence-based advice documents around possible interventions for COVID-19 provide useful support to those in clinical leadership positions and can help prevent dissemination of interventions for which there is no evidence to support their use.

## **Advice**

Arising from the findings above, HIQA's advice to the National Public Health Emergency Team is as follows:

- With respect to interventions for the prevention of progression to severe disease in patients with COVID-19 in community and ambulatory care settings:
  - The evidence identified and included in this review does not currently support the use of any pharmaceutical intervention outside of clinical trials.
  - No evidence was identified for non-pharmaceutical interventions.
- A large number of COVID-19 clinical trials are ongoing. Additional evidence will therefore continue to be reported both for novel interventions and those identified in this review. Consistent with current requirements:
  - Evidence regarding the effectiveness of therapeutic interventions, particularly for pharmaceutical treatments, must be subject to the highest standards of rigour.
  - As there are potential harms associated with all interventions, including non-pharmaceutical interventions, interventions must have a robust safety profile. They must be subject to the appropriate governance before they can be recommended for widespread use in the ambulatory or primary care setting. This is important given the serious risks of harm associated with unproven interventions.
  - If effectiveness evidence does emerge, all current due processes will be required, including with respect to potential reimbursement of drugs provided within the publicly funded healthcare system.
- The conclusions of this evidence summary should be clearly communicated to those working in ambulatory or primary care settings. All appropriate avenues for such communication should be considered, including GP webinars and other forums presented by the Irish College of General Practitioners.

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