INTERIM CLINICAL GUIDANCE FOR ADULTS WITH CONFIRMED COVID-19 IN BELGIUM
## TABLE OF CONTENTS

1. **Preliminary Note** ................................................................. 3
2. **Executive Summary** ............................................................. 5
3. **Precautions of Use & Additional Information** ............................. 7
4. **Report** .................................................................................. 10

1. **Belgian Recommendations for Supportive Care and Adjunctive Antiviral/Immunomodulatory Treatment for Confirmed COVID-19 Cases** ........................................... 10

   1.1 **Corticosteroids** .................................................................. 10
      1.1.1 Dexamethasone, system corticosteroids .................................. 10
      1.1.2 Inhaled corticosteroids ......................................................... 12

   1.2 **Remdesivir** ........................................................................ 13

   1.3 **Immunomodulatory Agents, Anti-Interleukin Therapy** ............... 16

   1.4 **Monoclonal Antibodies** ...................................................... 17
      1.4.1 Summary ........................................................................... 17
      1.4.2 Bamlanivimab ................................................................. 18
      1.4.3 Bamlanivimab + etesevimab ................................................. 18
      1.4.4 Casirivimab + imdevimab (Ronapreve, REGEN-COV) ............... 18
      1.4.5 Regdanvimab .................................................................. 19
      1.4.6 Sotrovimab ...................................................................... 20
      1.4.7 Tixagevimab and cilgavimab (AZD7442) ............................... 20

   1.5 **Convalescent Plasma** .......................................................... 22

   1.6 **Intravenous Immunoglobulines (IVIG)** ................................... 23

   1.7 **Janus Kinase Inhibitors** ....................................................... 23
      1.7.1 Baricitinib ........................................................................ 23
      1.7.2 Tofacitinib ....................................................................... 24
      1.7.3 Ruxolitinib ...................................................................... 25

   1.8 **Interferon** .......................................................................... 25

   1.9 **Chloroquine and Hydroxychloroquine** ..................................... 26

   1.10 **Lopinavir/Ritonavir** .......................................................... 27

   1.11 **Favipiravir** ........................................................................ 27

   1.12 **Molnupiravir (Lagevrio®)** ................................................... 28

   1.13 **Nirmatrelvir + Ritonavir (Paxlovid®)** ..................................... 28

   1.14 **Camostat Mesylate** ........................................................... 29

   1.15 **Fluvoxamine** ..................................................................... 30

   1.16 **Azithromycin** .................................................................... 31

   1.17 **Ivermectin** ...................................................................... 31

   1.18 **Colchicine** ....................................................................... 32

   1.19 **Aspirin** ............................................................................ 33
2 GENERAL NOTES........................................................................................................... 34
2.1 ACE INHIBITORS OR ARBS .......................................................................................... 34
2.2 PREGNANT WOMEN ................................................................................................. 34
2.3 CHILDREN ................................................................................................................. 34
2.4 ANTICOAGULATION IN COVID-19 PATIENTS ......................................................... 34
2.5 OXYGEN THERAPY IN COVID-19 PATIENTS ......................................................... 35
2.6 AMBULATORY CARE ................................................................................................. 35
■ ANNEXES ..................................................................................................................... 36
APPENDIX 1. AVAILABILITY OF REMDESIVIR ............................................................. 36
APPENDIX 2. SAFETY PROFILES .................................................................................... 36
APPENDIX 3. PRACTICAL ASPECTS CONCERNING ADMINISTRATION OF PAXLOVID®
(NIRMATRELVIR+RITONAVIR) ..................................................................................... 36
■ REFERENCES ............................................................................................................... 38
PRELIMINARY NOTE

COVID-19 is a mild viral illness in the vast majority of the patients (80%) but may cause severe pneumonitis and disseminated endothelitis (1) (and subsequent complications) with substantial fatality rates in elderly and individuals with underlying diseases.

This document is periodically revised to provide support to the diverse groups of Belgian clinicians (general practitioners, emergency physicians, infectious disease specialists, pneumologists, intensive care physicians) who face suspected/confirmed COVID-19 cases in Belgium. This guideline originally targeted primarily hospital care, but as the pandemic has evolved, and more potential treatment options against COVID-19 have emerged, the guideline as of version 26, provides guidance on specific treatments for COVID-19 in the hospital setting, but also in the ambulatory setting. The guideline still refers whenever necessary to other guidelines.

The guidance has been developed from March to December 2020 by a task force of Infectious Diseases Specialists (IDS): Dr Sabrina Van Ierssel, Universitair Ziekenhuis Antwerpen; Dr Nicolas Dauby, Hôpital Universitaire Saint-Pierre Bruxelles; Dr Emmanuel Bottieau, Instituut voor Tropische Geneeskunde (ITG), and Dr Ralph Huits, ITG, supported by Sciensano (Dr Chloe Wyndham-Thomas), the AFMPS/FAGG (Dr Roel Van Loock) and ad-hoc contributions from colleagues of other disciplines. Since January 2021, the COVID-19 therapeutic guideline has officially been taken over by the Belgian Society of Infectiology and Clinical Microbiology (BVIKM/SBIMC), and the new task force is composed of IDS representatives from all Belgian University Hospitals, with the additional collaboration of the Belgian Societies of Intensive Care Medicine and of Pneumology. The Belgian Health Care Knowledge Centre (KCE) is in charge of the coordination of the document since March 2023. The complete list of members is available below. This guidance is based on the best clinical evidence (peer-reviewed scientific publications) that is available at the moment of writing each update, and is purposed to be a “living guideline” which can be downloadable from the KCE Website via the following link. Keeping the guideline regularly updated is however particularly challenging due to the incredible speed of knowledge generation for this disease. Readers are warmly invited to send any additional comments, relevant publications, including from the grey literature, and contributions in priority to Dr Maya Hites (Maya.Hites@hubruxelles.be) and Dr Emmanuel Bottieau (ebottieau@itg.be). We take this opportunity to thank again the countless readers who, since this guideline was initially released, flagged the inconsistencies, typos or unclear text, as well as those who sent all types of contributions related to this rapidly evolving field.

Of note, this document will not describe in detail the generic and supportive management of COVID-19 (except if there are some pathogen-specific interventions). It is also not aimed at providing an extensive review on all potential investigational treatments in the pipeline.
Important

As a rule, only manuscripts ACCEPTED after a rigorous PEER-REVIEW process will be used for the strong recommendations in this guidance. Important (pre-publication) communications by well-established research groups will be however mentioned if the findings may strongly impact the clinical care within a rather short timeframe.

Use of off label or investigational antiviral or immunomodulatory drugs should be reserved to clinical studies/trials only and efforts are undertaken by the KCE to support non-commercial multicentric studies in Belgium. In addition, use of standardized case report forms is strongly encouraged during patient management, in order to obtain rapid feedback on safety issues and patient outcomes.

Members of the working group

Emmanuel André: Dept. Of Medical Microbiology, UZ Leuven
Emmanuel Bottieau: Dept of Clinical Sciences, Instituut voor Tropische Geneeskunde (ITG)
Nicolas Dauby: Dept. of Internal Medicine and Infectious Diseases, CHU-Saint-Pierre
Julien De Greef: Dept. of Internal Medicine and Infectious Diseases, Clin. Univ. Saint-Luc-UCLouvain
Pieter Depuydt: Dept. of Intensive Care Medicine, UZ Gent
Paul De Munter: Dept. of Internal Medicine, UZ Leuven
Fabian Desimpel: Expert doctor for KCE
Maya Hites: Clinic of Infectious Diseases, Hôpitaux Universitaire de Bruxelles (HUB)-Erasme
Frank Hulstaert: Expert doctor for KCE
Pascale Jonckheer: Expert doctor for KCE
Patrick Lacor: Dept. of Internal Medicine, UZ Brussel
Natalie Lorent: Dept. of Pneumologie, UZ Leuven
Jiska Malotaux: Dept. of Internal Medicine, UZ Gent
Sandrine Milas: Dept. Infectious Diseases CHU Charleroi
Sien Ombelet: Expert doctor for KCE
Sophie Servais: Dept. Of Hematology, CHU Liege
Fabio Taccone: Dept. of Intensive Care Unit, CUB-Erasme
Eva Van Braeckel: Dept. of Respiratory Medicine, UZ Gent
Sabrina Van Ierssel: Dept. of Internal Medicine, UZ Antwerpen
Roel Van Loock: DG PRE – Dept. of Assessors, FAGG – AFMPS

A Conflicts of Interest list for the members is available here.
EXECUTIVE SUMMARY

Table 1 – Supportive care & antiviral/immunomodulatory therapies for treatment of COVID-19 in outpatient and hospitalized patients

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Supportive Care</th>
<th>Additional therapy (Strength of recommendation - GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed mild or moderate COVID-19:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Mild disease: symptoms of COVID-19 without lower respiratory tract involvement such as dyspnea or abnormal chest imaging</td>
<td>Symptomatic treatment</td>
<td>Antivirals should be proposed to patients at high risk of severe progression and hospitalization (mainly severely immunocompromised patients). They can be considered for patients at moderate risk of hospitalization on an individual basis, after weighing the benefits and risks.(^a) Antivirals should be proposed <strong>AS EARLY AS POSSIBLE</strong> (targeting &lt; 5 days) from start of symptoms, in the following order:</td>
</tr>
<tr>
<td>➢ Moderate disease: clinical or radiological evidence of lower respiratory tract disease and SpO2 ≥94% or does not require supplemental oxygen</td>
<td></td>
<td>• Nirmatrelvir/ritonavir (Paxlovid®, oral), for 5 days, after careful evaluation of drug-drug interactions (strong recommendation for high-risk patients, conditional recommendation for moderate-risk patients; moderate quality of evidence)</td>
</tr>
<tr>
<td>Confirmed COVID-19 severe disease ≥ 1 of the following:</td>
<td></td>
<td>• Remdesivir (Veklury®, IV) for 3 days - only for high-risk patients when Nirmatrelvir/ritonavir is contra-indicated, <strong>only in hospital setting</strong> (conditional recommendation, moderate quality of evidence)</td>
</tr>
<tr>
<td>➢ Respiratory rate ≥30/min (adults); ≥40/min (children &lt;5y)</td>
<td>Optimal supportive care in hospital WARD (or ICU) Provide O₂ Administer LMWH according to BSTH guidelines, if not contra-indicated Carefully consider antibiotics or antifungals according to local epidemiology</td>
<td>Dexamethasone 6 mg once a day for up to 10 days (or until hospital discharge, if sooner), IV or PO (strong recommendation, high-quality evidence - 1A). If dexamethasone is not available, equivalent doses of corticosteroids can be used (hydrocortisone 150 mg/d or methylprednisolone 32 mg/d or prednisone 40 mg/d) (strong recommendation, moderate quality of evidence). Case by case decision for children and pregnant women pending additional results and with the respective specialists.</td>
</tr>
<tr>
<td>➢ Blood oxygen saturation ≤93% or requires supplemental oxygen</td>
<td></td>
<td>Remdesivir: Remdesivir (200 mg loading dose, on Day 1, followed by 100 mg per day for 5-10 days) (conditional recommendation, moderate certainty of evidence for patients not on high-flow oxygen).</td>
</tr>
<tr>
<td>➢ PaO₂/FI O₂ ratio &lt;300</td>
<td></td>
<td>Tocilizumab and other interleukin-6 blockers: consider early administration of IL6-receptor antagonists (tocilizumab 8 mg/kg IV with a maximum of 800 mg) in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (conditional recommendation, moderate quality of evidence), as long as there is availability of the drug (after prioritizing the drug for patients with cytokine release syndrome caused by chimeric antigen receptors T-cell medicines, giant cell arteritis,</td>
</tr>
<tr>
<td>➢ Lung infiltrates &gt;50% of the lung field within 24-48 hours</td>
<td></td>
<td>____________________________</td>
</tr>
</tbody>
</table>

\(^a\)Patients at **high** risk of hospitalization includes those with diagnosed immunodeficiency syndromes, those who have undergone solid organ transplant and are receiving immunosuppressants, and those with autoimmune illness receiving immunosuppressants.

\(^b\)Patients at **moderate** risk of hospitalization are those over 65 years, those with obesity, diabetes and/or chronic cardiopulmonary disease, chronic kidney or liver disease, active cancer, those with disabilities, and those with comorbidities of chronic disease.

\(^c\)Patients at **low** risk of hospitalization includes those who are neither moderate nor high risk. Most patients are low risk.

Adapted from Therapeutics and COVID-19: living guideline - World Health Organization (WHO) – v14 (2)
systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and severe rheumatoid arthritis), and taking into account that there is currently no reimbursement for the COVID-19 indication in Belgium.

A higher dose of dexamethasone (12 mg once a day) may be considered in patients with high needs in oxygen (≥10L/min or High Flow Oxygen Therapy (HFOT)), who are not receiving tocilizumab (weak recommendation, low quality of evidence).

**Baricitinib:** Consider the addition of baricitinib (4mg once daily for up to 14 days) in hospitalized patients with COVID-19 pneumonia (conditional recommendation, low quality of evidence). The request to the EMA for marketing authorization has been retracted by the firm.

**Tofacitinib:** Consider the addition of tofacitinib (10mg twice daily for up to 14 days) in hospitalized patients with pneumonia, when IL-antagonists and baricitinib are not available, after balancing individual risks (including a possible increased risk of thromboembolic events) and benefits (conditional recommendation, low quality of evidence). Current data suggests potential increase in adverse events in patients treated with tofacitinib. The EMA has not yet given approval of this drug for COVID-19.

**Dexamethasone** 6 mg IV (or equivalent doses of corticosteroids, see row above) once a day for up to 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists (strong recommendation, high-quality evidence).

Tocilizumab and other interleukin-6 blockers: Consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (conditional recommendation, moderate quality of evidence), as long as there is availability of the drug (after prioritizing the drug for patients with cytokine release syndrome caused by chimeric antigen receptors T-cell medicines, giant cell arteritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and severe rheumatoid arthritis), and taking into account that there is no current reimbursement for the COVID-19 indication in Belgium.

A **higher dose of dexamethasone** (12 mg once a day) may be considered in patients with high oxygen needs (≥10L/min or HFOT) or mechanical ventilation, who are not receiving tocilizumab (weak recommendation, low quality of evidence).

Remdesivir: recommendation against the initiation of Remdesivir in patients on mechanical ventilation or ECMO (conditional recommendation, low quality of evidence).

High-titer convalescent plasma: consider administration of high-titer convalescent plasma in patients with COVID-19–induced ARDS requiring mechanical ventilation, aim to administer within 48h after ventilation initiation (conditional recommendation, low quality of evidence).

<table>
<thead>
<tr>
<th>Confirmed COVID-19 critically ill disease</th>
<th>Optimal supportive care in ICU</th>
<th>Mechanical ventilation</th>
<th>Administer LMWH according to BSTH guidelines, if not contra- indicated</th>
<th>Specific prevention &amp; treatment of ARDS</th>
<th>Track secondary bacterial and opportunistic (Aspergillus) infections</th>
<th>Prevention of subsequent lung fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 of the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute Respiratory Distress Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Altered consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Multi-organ failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protracted COVID-19, mainly among lymphocyte B-cell depleted patients</th>
<th>Optimal supportive care in hospital WARD (or ICU)</th>
<th>Lack of evidence to support the use of a specific agent in this population so far.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prolonged viral shedding for weeks to months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ongoing symptoms of COVID-19, including progressive or relapsing hypoxemic pneumonia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARDS: Acute respiratory distress syndrome. LMWH: low molecular weight heparin
PRECAUTIONS OF USE & ADDITIONAL INFORMATION

General: Use paracetamol in first line (usual dosage), and NSAIDs with caution (if really required).

Dexamethasone: Usual contraindications. It is currently unknown whether the use of corticosteroids in COVID-19 is independently associated with an increased risk for bacterial or fungal infections. The use of dexamethasone may reduce the discriminatory potential of C-reactive protein (CRP) and procalcitonine (PCT) as biomarkers for the diagnosis of secondary bacterial infection.

Availability of antivirals for COVID-19 in Belgium:

<table>
<thead>
<tr>
<th>Name</th>
<th>Availability in Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir + ritonavir (Paxlovid®)</td>
<td>Paxlovid® has been reimbursed since Nov. 1, 2023.</td>
</tr>
<tr>
<td>Remdesivir (Veklury®)</td>
<td>Veklury® has been reimbursed since Oct. 1, 2023.</td>
</tr>
</tbody>
</table>

Nirmatrelvir/ritonavir (Paxlovid®):
- Warnings/precautions:
  For moderate renal impairment (eGFR ≥ 30 to < 60 mL/min): dose reduction to 150 mg of nirmatrelvir + 100 mg ritonavir.
  PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min)
  PAXLOVID is not recommended in patients with severe hepatic impairment (Child-Pugh Class C)
  Hepatic transaminase elevations have occurred in patients receiving ritonavir
  The use of Paxlovid® during pregnancy has not been formally tested
  Interactions:
  Ritonavir is a strong cytochrome P450 3A4 inhibitor, therefore Paxlovid should not be co-administered with drugs highly dependent on CYP3A or with potent CYP3A inducers. Check drug-drug interactions on the University of Liverpool website (link) and EMA (link).
Remdesivir (Veklury®):

**Contraindications:** hypersensitivity to active substance(s) or any of excipients

**Warnings/precautions:**

- Hepatic impairment: Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline.

- Renal impairment: Pharmacokinetics of remdesivir has not been extensively evaluated in patients with renal impairment. In patients with eGFR < 30mL/min, the benefits & risks are to be weighed.

- Possible bradycardia: Post-marketing study based on the World Health Organization pharmacovigilance database identified increased reports of serious bradycardia among patients treated with remdesivir. Remdesivir was the sole suspected drug among 93% of 88 patients. Following Pharmacovigilance Risk Assessment Committee (PRAC) advice, EMA has recommended to include bradycardia as a possible side-effect of Veklury. Nevertheless, a post-hoc safety analysis was carried out on data from the multicenter, randomized, open-label, controlled DisCoVeRy trial in hospitalized patients with COVID-19. Any cardiac adverse event occurring between randomization and day 29 in the modified intention to treat population randomized to either remdesivir or control group was considered. Results showed that remdesivir treatment was not associated with an increase of cardiac adverse events (serious or not) and regardless of severity in patients hospitalized with moderate or severe COVID-19 (HR 1.0, 95% CI 0.7-1.5, p= 0.98).

**Interactions:**

- Strong inducers of CYP2C8, CYP2D6 and CYP3A4 (e.g. rifampicin) may decrease plasma concentrations and are not recommended.

- Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

- Still limited information on drug interactions is available. Risk-benefit assessment should be made individually.

- Close monitoring of remdesivir toxicity or diminished efficacy of concomitant drugs is recommended. Check also for interactions with remdesivir at the drug-drug interactions on the University of Liverpool website.

More information on warnings/precautions of use in Veklury product information.

Registered for treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg). For pregnant women & children: compassionate use is possible, request on https://rdvcu.gilead.com/.

**Monoclonal antibodies (mAbs):** Treatment is authorized by the EMA, but they are not commercially available. In Belgium, mAbs can only be administered in the hospital setting, after authorization by a multidisciplinary team including at least an infectious disease physician. Currently, no available mAb is recommended to be used prophylactically or therapeutically.

Intrinsic resistance or decreased in vitro neutralisation has to be considered. We refer to the susceptibility summaries provided by The Stanford University https://covdb.stanford.edu/susceptibility-data/table-mab-susc/). Information on the VOC currently circulating in Belgium can be accessed via “Genomic Surveillance of SARS-CoV-2 in Belgium” (link), and data concerning VOCs circulating in Europe (Link).

Health care providers must have immediate access to medications to treat a severe infusion or injection reaction, such as anaphylaxis. Patients should be observed for at least one hour following completion of administration (IM or IV, in function of the drug).

Subcutaneous route should only be used when intravenous route is not feasible and will result in treatment delay (only for casirivimab+imdevimab).

Renal impairment: No dosage adjustment is required in patients with altered kidney function (including those on dialysis) or for geriatric patients.

Hepatic impairment: mAbs have not been studied in individuals with severe hepatic impairment.

Cardiovascular events or arterial thromboembolic events: A higher proportion of individuals who received tixagevimab/cilgavimab (EVUSHELD®), compared to placebo reported myocardial infarction and cardiac failure serious adverse events in the TACKLE and PROVENT trials. Furthermore, an observational trial using the VigiBase (the WHO’s individual case safety reports) database to assess the risk of arterial or venous thromboembolic events in COVID-19 disease in individuals 12 years old or older, exposed to EVUSHELD...
compared to other anti-SARS-CoV2 mAbs (casirivimab/imdevimab, bamlanivimab/etesivimab, and sotrovimab). There were 8,952 reports of patients who had received an anti-SARS-CoV2 mAb. There was an increased risk of reporting arterial and venous thromboembolic events in patients who received EVUSHELD compared to other mABs (3.25; 95%CI 1.73, 6.10, and 3.59; 95%CI 2.16, 5.96) (link). When giving this treatment for prophylaxis, weigh risks and benefits of this treatment in patients with cardiovascular risk factors (link).

**Pregnancy:** The risk of severe COVID-19 is increased in pregnant women and COVID-19 infection increases risks for adverse pregnancy outcomes. mAbs should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus, considering all associated health factors.

**Contraindications:** Hypersensitivity to monoclonal antibodies or to any of the excipients.

**Tociluzimab and Anakinra:** Caution must be exercised when used in patients with active concomitant (myco) bacterial and fungal infections and in chronically immunosuppressed patients. Alternative inflammatory markers instead of CRP (such as procalcitonin) may be used to monitor supra-infections in patients treated with IL-6 or 1-blockers.
1 BELGIAN RECOMMENDATIONS FOR SUPPORTIVE CARE AND ADJUNCTIVE ANTIVIRAL/IMMUNOMODULATORY TREATMENT FOR CONFIRMED COVID-19 CASES

As summarized in the executive summary table, we recommend that dexamethasone (or if not available, equivalent doses of corticosteroids) be considered as standard of care in severe and critical COVID-19 disease (grade 1A). Background data and rationale behind these recommendations are detailed here. Latest results concerning additional antiviral and immunomodulatory treatments are also covered hereunder.

Additional notes are also given on ACE inhibitors/ARBs, pregnant women, children, anticoagulation, oxygen therapy and ambulatory care.

1.1 Corticosteroids

1.1.1 Dexamethasone, systemic corticosteroids

Main message

Systemic corticosteroids (dexamethasone) are recommended for COVID-19 patients with severe disease. In case dexamethasone is not available, the WHO recommends using equivalent doses of other corticosteroids (6). See Executive summary Table 1 for details.

Available evidence in the hospital setting

Although treatment with systemic corticosteroids was initially not recommended (7,8), the availability of high-quality evidence demonstrates a reduction in mortality among COVID-19 patients with severe disease. Low dose dexamethasone (6 mg/day once daily for 10 days) is a treatment option which has been investigated in one of the UK-RECOVERY study arms. In this study, dexamethasone significantly reduced the overall 28-day mortality rate (age-adjusted rate ratio, 0.83 [95% CI 0.75 to 0.93]; P=0.001) (9). In a pre-specified subgroup analysis according to the level of respiratory support that the patients were receiving at randomization, there was a trend showing the greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation (11.5 by chi-square test for trend). Compared with standard of care, dexamethasone reduced incidence of death in ventilated patients (29.3% vs. 41.4%, rate ratio 0.64 [95% confidence interval 0.51 to 0.81]) and in other patients receiving oxygen only (23.3% vs. 26.2%, 0.80 [0.70 to 0.92]). No evidence of benefit for patients who did not require oxygen was found, and patients outside the hospital setting were not included in the study. In a sub-group analysis, dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with more recent symptom onset (12.3 by chi-square test for trend). Based on this survival benefit in the sickest patients, the manageable toxicity of low-dose/short-course dexamethasone in hospitals and the strong biological plausibility of an anti-inflammatory treatment in the second phase of COVID-19 infection, the Belgian Clinical Treatment Guidelines task force has recommended since version 12 low-dose dexamethasone for admitted patients requiring oxygen, in particular requiring mechanical ventilation and with a symptom onset >7 days. Following the publication of the RECOVERY results, three other large RCTs evaluating various doses and types of steroids in critical COVID-19 stopped patient inclusion prematurely before reaching the respective target sample sizes, i.e. REMAP-CAP (multicountry) (10), CoDEX (Brazil) (11), and CAPE COVID (France) (12). The results of RECOVERY, of the last 3 published (“incomplete”) RCTs and of another three ongoing smaller trials were then pooled and meta-analyzed by the WHO REACT working group (6). The conclusion was robust throughout all trials (n=678 in total versus 1025 in placebo/usual care arm, all critically ill patients): administration of systemic corticosteroids in critically ill patients with COVID-19 is associated with decreased 28-day mortality (0.66 [95% CI 0.53-0.82; p<0.001). This association was similar for dexamethasone and hydrocortisone, for higher versus lower doses of steroids, and in admitted patients with fewer or greater than 7 days of symptoms, requiring oxygen either through mechanical ventilation or not. While exact details concerning the implementation in clinical practice is lacking, the consistent findings of benefit provide definitive data that corticosteroids should be first-line treatment for critically ill patients with COVID-19 (13). A study confirmed that corticosteroids should not be administered to hospitalized patients with COVID-19 who do not require oxygen. Indeed, in an observational cohort of 19,973 patients admitted to the hospital within 14-days of a positive PCR or antigen test for SARS-CoV2, an inverse probability of treatment weights was used to balance exposed to unexposed groups, and a Cox proportional hazards model was used to determine 90-day
all-cause mortality. Patients on no oxygen who received dexamethasone had a 76% increased risk for 90-day mortality (HR 1.76, 95% CI 1.47 to 2.12) (14).

A living Cochrane Systematic Review and Meta-Analysis on the use of systemic corticosteroids in COVID-19 thus far included 11 RCTs in 8075 participants but restricted outcome analysis to 9 RCTs (up to date until April 2021). The main conclusions were that systemic corticosteroids plus standard care as compared to standard care alone probably reduced all-cause mortality slightly (risk ratio 0.89 (CI 0.80-1.00) and may increase ventilator-free days (mean difference 2.6d, CI 0.7-4.5) (15). Importantly, 42 ongoing studies and 16 studies reported completed or terminated without yet published results were identified, suggesting that effect estimates and certainty of the evidence may change in the future.

The COVID STEROID 2 trial randomized 1000 patients with severe to critical COVID-19 (supplemental oxygen with a flow rate of at least 10L/min or receiving mechanical ventilation) between 6mg and 12mg dexamethasone. In the 12mg dexamethasone group, median number of days alive without life support (adjusted mean difference -1.3d (0-2.6)) and 28-mortality (adjusted relative risk 0.86 (0.68-1.08)) were lower. Although both endpoints failed to reach statistical significance, the accompanying editorial suggested a clinically meaningful treatment effect of higher dose corticosteroids in more severely ill COVID-19 patients [COVID STEROID 2 Trial Group]. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia (16,17). In addition, a pre-planned Bayesian analysis of the COVID STEROID 2 trial data found high probabilities of benefit and low probabilities of clinically important harm with dexamethasone 12mg versus 6mg up to 60 days after inclusion. Longer term outcome, as expressed by mortality and health-related quality of life at 180 days, was however not significantly different between higher and standard dose dexamethasone groups, although the results were again mostly compatible with a benefit from 12mg, and an absolute 3% or more increase of mortality could be rejected with 99% certainty (18). Finally, the results of the COVID STEROID 2 trial raise the possibility that benefit from IL-6 receptor antagonists may be less substantial when co-administered with this higher dose of corticosteroids, as mentioned in the same editorial (17).

Additional studies comparing different doses of corticosteroids in COVID-19 have been published. A randomized monocentric trial carried out in Iran in 144 hospitalized patients with moderate to severe COVID-19 evaluated the efficacy and safety of different doses of dexamethasone (8 mg once daily, 8 mg twice daily, and 8 mg three times daily for up to 10 days or hospital discharge). Higher doses of dexamethasone resulted in an increase in adverse events, a lower clinical response, and shortened survival compared to lower doses of dexamethasone (19). A multicenter RCT randomized 546 patients between standard (6mg) and high (20mg) dose dexamethasone and different oxygenation strategies (low flow oxygen, high flow oxygen and CPAP) in a 2x3 factorial design; no differences in 60-day mortality were observed between patients receiving 6mg versus 20mg dexamethasone (20).

A pilot RCT was done using biomarker (CRP) guided approach to steroid dosing. Forty-one patients were included: 19 in the intervention arm, and 22 in the usual care arm. The study was ongoing when the results of the RECOVERY trial were published. After that the patients in the standard of care arm received a fixed dose of steroids. Only 50% of the patients in the usual arm received steroids. When only patients on steroids were analyzed, the intervention arm (n=17) had less cumulative steroid exposure [median 122 (102.0, 160.0) mg, p=0.005], more oxygen-free days [23 (20, 25) versus 17 (8, 22), p=0.032] and no difference in hospital-free days [21 (18, 22) versus 17 (7, 21), p=0.06] than the usual care arm (n=11). The study showed that the CRP-based dosing was feasible and safe. A large (multicenter) RCT is warranted to be able to determine an effect on patient outcome (21).

In addition, observational studies have addressed the questions which subgroups of patients with severe COVID-19 benefit (most) and which experience harm from corticosteroids. A two-class latent class analysis of 483 patients with COVID-19 associated ARDS identified a differential response to corticosteroids with a lower risk of death in the hyperinflammatory phenotype and a higher risk of death in the hypo-inflammatory phenotype (22). In a Spanish multicenter observational study including 4226 patients with COVID-19 admitted to the ICU, a beneficial effect of corticosteroids was observed in the overall population; however early administration (<7 days since symptom onset) was associated with a higher risk of 90-days mortality (23).

**Notes on treatment with systemic corticosteroids**

It is currently unknown whether the use of corticosteroids in COVID-19 is independently associated with an increased risk for bacterial or fungal infection. A systematic review with meta-analysis complemented the 7 RCTs analyzed in (6) with 37 retrospective observational studies, covering 20,197 patients (24). Diverse corticosteroid regimens were investigated, most of which consisted of methylprednisolone; 16/29 and 11/29 studies used respectively high (>1mg/kg prednisolone) and lower (<1mg/kg prednisolone) doses. A trend towards more antibiotic use and more infections (6 studies) was noted; however overall pooled estimates...
showed a reduced mortality in the corticosteroid-treated patients (OR 0.72; 0.57-0.87), which is in a range similar to that found in the WHO REACT working group meta-analysis (6). A prospective study with serial assessment of C-reactive protein (CRP) and procalcitonin (PCT) in COVID-19 patients found a lower discriminative value of both biomarkers for the early detection of secondary bacterial infections in patients treated with dexamethasone with and without tocilizumab (25).

The risk versus benefit of late corticosteroid therapy in patients with COVID-19 associated ARDS is currently not known. A post-hoc analysis of a multicenter dataset of 348 patients with moderate to severe ARDS associated with COVID-19 admitted to 21 French and Belgian ICUs, comparing with and without corticosteroid-treatment after 13 days of symptom onset did not find a difference in ICU mortality (HR 1.44; 0.83-2.50) or duration of mechanical ventilation (HR 0.89; 0.60-1.33) (26). No studies have addressed the question whether a prolonged course or a second course of corticosteroids influence the outcome in COVID-19 patients who remain ventilator dependent following a standard course of corticosteroids as provided in the RCTs. A systematic review and trial sequential meta-analysis was performed analysing the use of corticosteroids in patients with ARDS due to COVID-19 and non-COVID-19 related etiology. The use of corticosteroids was found to probably reduce 28-d mortality (RR 0.82; 0.72-0.95) regardless of etiology, and to probably reduce the duration of mechanical ventilation (mean difference 4d fewer, 2.5-5.5), but the optimal information size was not reached in the trial sequential analysis. Among the pooled analysis of COVID-19 and non-COVID-19 patients, those who received >7d of corticosteroids had lower mortality than those who received a ≤7d course (p=0.04) (27).

Effects of low-dose and short-course corticosteroids on risk of Strongyloides reactivation is not well known. Nevertheless, for high-risk patients, such as those originating from Strongyloides endemic areas, empirical ivermectin treatment should be considered before, or early during, corticosteroid treatment (28).

**Available evidence in the ambulatory setting:** While exact details concerning the implementation in clinical practice is lacking, the consistent findings of benefit provide definitive data that systemic corticosteroids should be first-line treatment only for severely and critically ill patients with COVID-19 (13).

### 1.1.2 Inhaled corticosteroids

**Available evidence in the hospitalized setting**

No data

**Available evidence in the ambulatory setting**

The possible benefit of inhaled corticosteroids in early COVID-19 (<7 days after symptom onset) was investigated in a phase-II open label RCT in the UK (29). The trial was stopped early because of a reduced number of new cases. Independent statistical review concluded that the study outcome would not change with further participant enrolment. The patients in the budesonide group had a significantly lower probability of an urgent care visit (15% vs 3%). The number needed to treat to avoid an urgent care visit was eight. Self-reported clinical recovery was shortened by 1 day (median 7 days [95% CI 6–9] vs 8 days [7–11]; log-rank test p=0.007). This is the first published trial evaluating inhaled corticosteroids in COVID-19. Several similar trials are still ongoing.

The PRINCIPLE trial investigated 2x800μg inhaled budesonide added to usual care in (suspected) COVID-19 patients in the community, aged ≥65y or ≥50y with co-morbidities and ≤14d symptoms. The study ran from November 2020 until March 2021 and included 4700 participants; a Bayesian primary analysis model included data from 2530 patients with confirmed COVID-19. This analysis found a shorter time to self-reported recovery (minus 3d; CI: 1-5.4) in the budesonide arm, as well as a lower rate of hospital admission or death (2%, 0.2-4.5%), the latter without however reaching the prespecified threshold of superiority. In prespecified subgroup analyses, the budesonide effect was not modified by symptom duration before randomization, baseline symptom severity, age or comorbidities. Few serious adverse events were reported, and there was no observed difference between the budesonide group and the usual care group (30).

Results of a phase-III RCT placebo-controlled trial on inhaled ciclesonide, including 400 non-hospitalized patients with symptomatic COVID-19, showed no significant difference in time to alleviation of COVID-19 related symptoms (primary endpoint) although a reduction in the number of hospitalizations or emergency department visits was observed in one of the secondary endpoints (31). The CONTAIN trial is a phase II placebo controlled RCT on inhaled ciclesonide in patients with predominantly respiratory symptoms (fever, cough, dyspnea). The trial was stopped early because of dropping numbers of new inclusions when the rate of vaccination was rapidly increasing. 203 patients were included in the modified intention-to-treat population, randomised 1:1 inhaled an intranasal ciclesonide vs placebo. There was no
statistically different in symptom resolution on day 7, the primary endpoint (40% vs 35%, absolute adjusted risk difference 5.5% (95% confidence interval −7.8% to 18.8%). The trial included mostly young people without comorbidities who are already a low-risk population. It is also possible that the study was underpowered to show significant results because it was stopped early. Currently however there is insufficient evidence to support the use of inhaled steroids (32). The COVERAGE trial is another open-label, RCT in outpatients with documented COVID-19 with risk factors for aggravation, and with symptoms for ≤ 7 days where patients were randomized to the control arm or other treatment arms, one of which was inhaled ciclesonide. In this arm of the trial, there were 217 participants, all with at least one co-morbidity. No significant difference was observed in the intention-to-treat population in reaching the primary end-point of COVID-19 worsening by day 14 (12/106 (11.3%, 95% CI: 6 to 18.9%) in the control arm vs. 14/106 (13.2%, 95% CI: 7.2 to 21.2%) in the ciclesonide arm (33).

A meta-analysis including four RCTs on the use of inhaled corticosteroids in outpatients with COVID-19 found a significant effect on the resolution of symptoms at day 14, although this was smaller in the placebo-controlled studies as compared to the open label studies; a reduced probability of hospitalization with inhaled corticosteroids was only observed in the open label studies, suggesting an important placebo effect (34).

Results of the ACTIV-6 trial showed that treatment with inhaled fluticasone furoate for 14 days did not result in a shorter time to recovery than placebo among outpatients with COVID-19 (HR 1.01, 95% CI: 0.91 to 1.12) (35).

Furthermore, a trial investigated if early initiation of inhaled beclomethasone 1200 mcg in patients with asymptomatic, mild or moderate COVID-19 reduces disease progression to severe COVID-19. A total of 385 participants were randomised to receive beclomethasone or placebo, and beclomethasone did not reduce disease progression to severe COVID-19 (36).

In advice dated on 27/5/2021, the EMA considered the evidence published thus far as insufficient to recommend the use of inhaled corticosteroids in COVID-19, as the possibility of causing harm to patients not requiring additional oxygen, cannot as yet be excluded (link).

1.2 Remdesivir

Main message

The WHO issued a conditional recommendation for the use of remdesivir (RDV) in hospitalized patients with moderate to severe COVID-19, due to data showing a minimal reduction in mortality (low certainty of evidence) and a more significant reduction in the need for mechanical ventilation (moderate certainty of evidence). Furthermore, they have given a conditional recommendation against its use in patients with critical COVID-19 (2).

Available evidence in the hospital setting

RDV seemed promising in vitro and in non-human primate models (37). An initial Chinese trial did not show any survival benefit with RDV, but the study could not include enough cases and was discontinued at the end of the local epidemic (38). In this study (where median delay from symptom onset to enrolment was quite long, 11 days in the RDV group), there was no effect of RDV on viral load over time in both upper and lower respiratory tract specimens, suggesting the absence of antiviral effect.

A final report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US was published (39) confirming a faster recovery in RDV-treated hospitalized COVID-19 patients with evidence of pneumonia (n=541) compared to patients given placebo (10 days instead of 15 days; recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p<0.001). The benefit was most apparent in those COVID-19 patients receiving low-flow oxygen, the largest group of patients included in the study, and when RDV was given before the 10th day of symptom onset. Results were not conclusive for other groups of patients (those not requiring supplemental oxygen, or in patients requiring mechanical ventilation). No statistical difference was seen for mortality by Day 15 (6.7% mortality versus 11.9%) and by Day 29 (11.4 versus 15.2%), but there was a positive trend compared to placebo (hazard ratio: 0.73 95% CI 0.52 to 1.03).

In addition, a randomized, open-label, phase 3 trial, comparing 5-day and 10-day treatment with RDV in patients with severe/critical disease (oxygen requirement), did not find a significant difference in efficacy between these two treatment durations. After adjustment for baseline imbalances in disease severity (patients assigned to 10-day course had significantly worse clinical status than those in the 5-day group), outcomes were similar as measured by a number of endpoints: clinical status at day 14, time to clinical improvement, recovery, and death from any cause. Post-hoc analysis showed that patients receiving mechanical ventilation or ECMO may benefit from 10 days of RDV treatment. Further evaluation of this subgroup and other high-risk
groups, such as immunocompromised persons, is needed to determine the shortest effective duration of therapy in these patients (40).

A third RCT sponsored by Gilead (Spinner et al.) assessed the role of RDV in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) (41). The patients (n=584) were randomized 1:1:1 to 10-day course of RDV, 5-day course of RDV and standard of care. Mortality was low (1%). A better clinical status on day 11 after treatment initiation was observed with the 5-day course but not the 10-day course. The clinical significance of this finding remains uncertain as the patients in the 5-day and 10-day courses received almost the same number of doses of RDV (5 and 6, respectively).

It is important to highlight that in both the ACTT-1 and Spinner trials, no impact of RDV on viral shedding was reported. In both trials, the median duration of symptoms before enrollment was 9 days, limiting the potential for a significant antiviral effect as was also observed in the Wang et al. trial (38).

In December 2020, results from the SOLIDARITY multicenter worldwide pragmatic trial were published, showing no overall clinical benefit of RDV in hospitalized patients with COVID-19. RDV was evaluated in 2743 patients, compared to 2708 controls. In a meta-analysis of the 4 published trials on RDV, a weighted average of the results from all trials yielded a rate ratio for death (RDV vs. control) of 0.91 (95% CI, 0.79 to 1.05). However, in the subgroup of patients receiving no mechanical ventilation at time of randomization, the rate ratio for death was 0.80 (0.63-1.01) (42). The WHO issued a conditional recommendation against the use of RDV in hospitalized patients, regardless of the severity, as there was no evidence that RDV improved survival and other outcomes in these patients. Nevertheless, WHO continued to endorse including patients in trials with RDV to establish with certainty whether RDV had a positive effect on survival in mild to moderate, hospitalized COVID-19 patients. The Solidarity trial and its’ European sister trial, DisCoVeRy continued to randomize mild to moderate hospitalized COVID-19 patients to receive RDV vs. standard of care until the 27th and 29th of January 2021, respectively. Inclusions into the RDV arm were stopped due to futility in severe, but also mild to moderate, hospitalized COVID-19 patients. The results of the DisCoVeRy trial, with 857 inclusions, showed no significant effect on viral kinetics, clinical progression or outcome in RDV treated patients compared to those treated with standard of care (43). Nevertheless, a paper on the modelling of the antiviral efficacy of RDV in COVID-19 hospitalized patients, based on nasopharyngeal normalized viral loads collected over the 29 days following randomization from 665 patients who participated in the DisCoVeRy trial, showed a 1-day reduction in time to SARS-CoV2 clearance compared to SoC (with large inter-individual variabilities). Results differ from the published results on viral kinetics from the DisCoVeRy trial, as analyses were stratified on time of treatment initiation, and on viral load at randomization. The impact was greater in patients with a high viral load at randomization (44). A meta-analysis of the 5 published RCTs on RDV vs. control has also shown the modest effect of RDV in hospitalized patients. Patients in the RDV treatment group had a greater likelihood of hospital discharge, and clinical improvement was more rapid than the control group, yet no effect was observed on mortality (45). Another retrospective, multicenter study published by Gilead, based on the US Premier Healthcare inpatient database in which 28,855 RDV-treated patients (within first 48-hours of hospitalization) were matched with 16,687 patients who did not receive RDV during their hospitalization, showed a statistically significant reduction in mortality by day 14 and day 28 in the overall population and in most baseline oxygen subgroups, except for those who needed high-flow oxygen at baseline (46). In a pragmatic, randomized, open-label, multicenter Canadian trial in hospitalized patients with COVID-19, comparing standard of care to RDV plus standard of care, no significant effect on in-hospital mortality was observed (18.7% vs. 22.6%; RR 0.83 (95% CI 0.67 to 1.03)). However, there was significantly less need for mechanical ventilation in patients not mechanically ventilated at baseline in the RDV plus standard of care arm compared to standard of care arm alone (8% vs. 15%; RR 0.53 (95% CI 0.38 to 0.75)) (47). Finally, in a nationwide population-based cohort study in Denmark, comparing death within 30 days of hospitalization and need of mechanical ventilation in two cohorts of patients hospitalized with COVID-19 from February to December 2020 (those who received RDV + DXM to SoC alone (no RDV + DXM)), showed that the 30-days mortality rate in the 1694 patients who received RDV and dexamethasone was 12.6%, compared to 19.7% in the 1053 patients who received SoC alone (OR of 0.47 (95% CI: 0.38-0.57). A reduction of progression to mechanical ventilation was also observed (OR 0.36; 95% CI: 0.29-0.46). Nevertheless, the SoC cohort were patients hospitalized from February to May, 2020, and the RDV plus dexamethasone cohort were patients hospitalized from June to December, 2020, suggesting the potential bias of time (48). The final results of the WHO SOLIDARITY trial have been published, showing a slight benefit in terms of halting disease progression and improving survival in patients treated with RDV compared to SoC. A total of 14,304 patients participated in the trial from 35 different countries around the world. 11.9% of patients not ventilated initially, and who received RDV, died, compared to 13.5% assigned to control (RR 0.86 [0.76–0.98], p=0.02) and 14-1% versus 15-7% progressed to ventilation (RR 0.88 [0.77–1.00], p=0.04) (49). This new data has resulted in changes in the WHO living guidelines. They have given a conditional recommendation to treat patients with severe COVID-19 with RDV, based on a low certainty of evidence to reduce mortality, and a moderate certainty to reduce the need for mechanical ventilation. Furthermore, they have given a conditional recommendation against its use in patients with critical COVID-19.
RDV has been explored in different patient populations. A retrospective, monocentric, propensity score-matched observational study of RDV in 31 patients with severe kidney disease, showed that when compared to a matched cohort of 31 patients that did not receive RDV, there was no increase in adverse events (cardiological, neurological, kidney or liver), except for a significant increase in risk of hyperglycemic events. This risk was partially attributed to the increased use of dexamethasone in the RDV treated cohort (53).

RDV was also well tolerated (16% of serious adverse events), and recovery rates were high in 86 pregnant and post-partum women with severe COVID-19 (90% were discharged alive amongst the pregnant cohort, and 84% amongst the post-partum cohort), who received the drug via a compassionate use program (54). A review of RDV in pregnant women with COVID-19 also concluded that there is a paucity of data on RDV in this patient population. Nevertheless, RDV appears to be well tolerated in the second and third trimesters of pregnancy, with a low risk of serious adverse events. No conclusions could be made concerning the administration of RDV to patients during the first trimester of pregnancy, due to the paucity of data (55).

Available evidence in the ambulatory setting

Although RDV’s place in the therapeutic arsenal against COVID-19 remains controversial, on December 16, 2021, EMA adopted a positive opinion recommending RDV in COVID-19 patients not requiring supplemental oxygen and at increased risk of progressing to severe COVID-19.

In a randomized, double-blind, placebo-controlled, multi-centre clinical trial evaluating treatment with RDV in an outpatient setting, 562 unvaccinated adult patients with confirmed COVID-19 and at least 1 risk factor for disease progression, were randomized 1:1 to IV remdesivir (200mg on d1, 100mg on d2 and d3) or placebo plus SoC. Patients with renal insufficiency were not excluded from the trial except if they weighed < 48 Kgs. Stratification was done by residence in a skilled nursing facility (yes/no), age (<60 vs ≥60) and region (US vs ex-US). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3,6) days; median viral load was 6.3 log10 copies/mL at baseline. The study was terminated early for administrative reasons, and less than half of the planned original enrollment was achieved. The primary endpoint was the proportion of patients with COVID-19 related hospitalization or all-cause 28-day mortality. Events occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) patients concurrently randomized to placebo, demonstrating an 87% reduction in COVID-19-related hospitalization or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28 in either group (56). These results support the use of antiviral treatments very early on in the course of COVID-19 infection and open the discussion concerning the possibility of administering a short-course (3-days) RDV treatment to patients with chronic renal insufficiency. 18 patients with mild to moderate chronic renal disease participated in the PINETREE trial.

An oral formulation of RDV, VV116 (a deuterated remdesivir hydrobromide) was just compared to nirmatrelvir-ritonavir in a phase 3, noninferiority, randomized trial during the SARS-CoV2 B.1.1.529 (omicron) variant outbreak, in China in 822 adults with mild-to-moderate COVID-19 at risk for progression. Approximately 25% of the patient population was not vaccinated against SARS-CoV2. Only one patient with an immunosuppressive disease, or treatment was included in the trial. No significant difference was observed between the two groups, concerning time to sustained symptom resolution and to a first negative SARS-CoV2 test. No participant died or progressed to severe COVID-19 by day 28 (57).

The WHO issued a conditional recommendation for the use of remdesivir (RDV) in outpatients with non-severe COVID-19 at high risk of hospitalization (moderate certainty evidence for decreased admission to hospital) (2).
1.3 Immunomodulatory agents, anti-interleukin therapy

Main message

Immunomodulatory agents are a varied group of drugs that may prevent or dampen hyper-inflammatory responses which are associated with clinical deterioration and mortality among COVID-19 patients (58,59). Potential adverse events, immunosuppression and drug interactions need to be carefully taken into consideration when choosing to treat patients.

Available evidence in the hospital setting

Several interleukin (IL) and complement blockers used in inflammatory diseases such as giant cell vasculitis or rheumatoid arthritis have been proposed for repurposing based on limited clinical experience and small observational studies. These drugs include tocilizumab (IL-6-receptor antagonist) (60,61), sarilumab (IL-6 receptor antagonist), siltuximab (anti-IL-6) and anakinra (IL-1-receptor antagonist), as well as complement inhibitors such as C3 and C5 inhibitors, C5a receptor inhibitors and C1 esterase inhibitors. Eight randomized trials assessing the use of tocilizumab (TCZ) in hospitalized COVID-19 patients have been published (62–64). These trials were highly heterogeneous regarding the severity of the patients included.

A WHO-initiated meta-analysis on 27 randomized trials showed that IL-6 antagonist was associated with lower 28-day all-cause mortality in patients hospitalized for COVID-19 (65). Importantly, a significant mortality benefit was only found when IL-6 receptor antagonists were co-administered with glucocorticoids, and most evident among patients who received respiratory support with oxygen by nasal cannula, face mask, high-flow nasal oxygen or non-invasive ventilation versus those who required invasive mechanical ventilation (65,66). There was not a clear benefit associated with anti-IL-6 among patients who already required mechanical ventilation at the time of randomization. Data were strongest for tocilizumab as compared to sarilumab (less available evidence). The accompanying editorial however points out some limitations to this meta-analysis, the most important being the lack of accounting for the baseline risk of death (66). This might explain the finding that COV-AID, a study carried out in a Belgian setting, showed no added benefit from anti-IL-6 treatment (67).

Most international guidelines, including those of the European Respiratory Society (ERS), the National Institutes of Health (NIH), and the Infectious Diseases Society of America (IDSA) have now formulated a conditional recommendation, with moderate certainty of evidence, towards the addition of tocilizumab to standard of care (i.e. steroids) rather than standard of care alone, in hospitalized adults with progressive severe (SpO2 ≤94% on room air, including patients on supplemental oxygen) or critical (mechanical ventilation and ECMO) COVID-19 who have elevated markers of systemic inflammation (68). In the largest trial on treatment with tocilizumab, the criterion for systemic inflammation was defined as CRP >75 mg/L. Both RECOVERY and REMAP-CAP (the two tocilizumab trials that reported a benefit) initiated treatment early (randomization at median of two days of hospitalization in RECOVERY; <24 hours in the ICU for REMAP-CAP), suggesting tocilizumab may be more beneficial in people with early, rapidly progressive disease. The recommended dosage of tocilizumab is 8mg/kg IV with a maximum dose of 800mg.

The product RoActemra (tocilizumab) was approved on the 17th of December, 2021 for treatment of hospitalised adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation (link). However, it must be mentioned that there are currently significant drug shortages of this drug, and there are patients who depend on this drug for other indications than COVID-19. It is in this light that the drug must be prioritized. It is recommended to give priority to patients to receive this drug in the following order: patients with cytokine release syndrome caused by chimeric antigen receptors T-cell medicines, giant cell arteritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and severe rheumatoid arthritis). Furthermore, it is important to note that there is currently no reimbursement for administration of tocilizumab in COVID-19 patients in Belgium.

A double-blinded, RCT study in 1060 patients hospitalized for COVID-19, included across 37 sites in Italy and Greece, also showed a clear outcome benefit in patients with a concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥ 6ng/mL who received anakinra (100 mg QD sub-cutaneously for 7-10 days) compared to those who received standard of care + placebo. 50.4% (204/405) of patients receiving anakinra had fully recovered with no viral RNA detected on day 28 compared to 26.5% (50/189) of patients receiving placebo, and 3.2% (13/405) and 6.9% (13/189) of patients in the anakinra and placebo arms, respectively, died. Therefore, the unadjusted proportional odds of having a worse score on the 11-point WHO-CPS at day 28 with anakinra was 0.36 versus placebo (95% confidence interval (CI) 0.26–0.49, P<0.0001. Because suPAR measurement is not widely available in the routine laboratory setting, the authors performed a post-hoc analysis to identify other tools to identify patients who might benefit from anakinra treatment. They found that predictors of favorable responses to anakinra are a combination of at least two measures of of
CRP >50 mg/L, neutrophil-to-lymphocyte ratio (NLR) >5.5, ferritin >700 ng/ml and aspartate aminotransferase (AST) > 44 U/L (69). Nevertheless, this prediction score remains to be validated in a prospective study.

Kineret (anakinra) has also just been approved on the 16th of December, 2021 for treatment of COVID-19 in adult hospitalized patients with pneumonia who are at risk of developing severe respiratory failure, and who have a measured plasma concentration of suPAR ≥ 6ng/ml (link). Currently, the measurement of suPAR cannot be carried out in a routine fashion in Belgian laboratories.

In August 2022, the results of the proof-of-concept ZILU-COV trial, carried out in Belgium, were published. Hospitalized COVID-19 patients with signs of systemic inflammation and hypoxemia (n = 81) were randomized to receive zilucoplan or SoC. The administration of C5 inhibition was considered safe and was associated with a (non-significant) trend to a better respiratory and clinical outcome (70). However, these results do not support the use of complement inhibition in routine clinical practice.

Notes on treatment with immunomodulatory agents

Caution must be exercised when used in patients with active concomitant (myco-) bacterial and fungal infections and in chronically immunosuppressed patients. Alternative inflammatory markers instead of CRP (such as procalcitonin) may be used to monitor infectious complications in patients treated with IL-6-blockers.

Available evidence in the ambulatory setting:

No data.

1.4 Monoclonal antibodies

Main message

After weighing the pros and cons, the working group no longer recommends administration of monoclonal antibodies (mAbs) for either prophylactic or therapeutic use, even in very immune-suppressed patients.

Since the emergence of VOC (in particular, the Omicron variant), a number of mAbs have shown an in-vitro decrease in their neutralisation capacity. In-vitro data show no or weak neutralization of VOCs by currently available mAbs (71–73). We would like to refer to the susceptibility summaries provided by The Stanford University (https://covdb.stanford.edu/susceptibility-data/table-mab-susc/) and the NIH COVID-19 susceptibility table (https://www.covid19treatmentguidelines.nih.gov/tables/variants-and-susceptibility-to-mabs/).

It is essential to regularly consult the monitoring data concerning the circulating VOC. Information on the VOC currently circulating in Belgium can be accessed via “Genomic Surveillance of SARS-CoV-2 in Belgium” (link), and data concerning VOCs circulating in Europe (Link).

Available evidence

Dozens of mAbs targeting the Receptor Binding Domain (RBD) of the spike protein (S protein) (with the exception of sotrovimab which does not directly block the ACE2 receptor) have been developed and more than 50 trials are being conducted (74). Mutations in the spike protein of SARS-CoV-2 variants may impact the expected clinical efficacy of monoclonal antibody therapies.

Given the long half-life, a single injection (mostly intravenous, occasionally subcutaneous or intramuscularly) is generally used (75).

It is important to stress that very early administration of this treatment is essential, even if this might be challenging to organize because it requires appropriate hospital infrastructure and excellent collaboration with primary care for timely appropriate referral.

1.4.1 Summary

Monoclonal antibodies are no longer recommended for COVID-19 patients with mild to moderate disease at high risk of clinical deterioration, even if these therapeutics are administered early after infection onset.

Intrinsic resistance to monoclonal antibodies should also be considered, particularly in light of the successive emergence of variants. The mAbs have been less studied for treatment in immunocompromised patients (a group for whom such treatments appear attractive), in vaccinated individuals or persistent shedders. Furthermore, efficacy studies against new emerging SARS-CoV-2 variants are necessary to monitor efficacy of these treatments as the genomic landscape evolves.
1.4.2 Bamlanivimab

Available evidence in the hospital setting

A phase II RCT with bamlanivimab (trial conducted by the ACTIV-3/TICO LY-CoV555 Study Group) in hospitalized patients, bamlanivimab (co-administered with remdesivir) did not demonstrate any clinical benefit (76).

Available evidence in the ambulatory setting

A phase II RCT with bamlanivimab (BLAZE-1, NCT04427501) in mild and moderate COVID-19 outpatients showed promising results on viral decline, symptom resolution and hospitalization (77). Several US real world case-control studies have shown that bamlanivimab treatment prevents hospitalization among mild to moderate COVID-19 infections. However, these studies were performed between November 2020 and February 2021, when few bamlanivimab resistant variants of concern (VOC) were in circulation (78,79). Due to the current circulation of Omicron variants, the prescription of this mAbs is no longer recommended.

1.4.3 Bamlanivimab + etesevimab

Available evidence in the hospital setting: No data.

Available evidence in the ambulatory setting: The phase 2/3 portion of BLAZE-1 outpatients treated with the combination of bamlanivimab and etesevimab, administered together in a single infusion, showed a significant reduction in viral load on day 11, while no significant change was seen on viral load with bamlanivimab alone. Among secondary endpoints, there were no consistent differences between the monotherapy and the combination therapy versus placebo for the other measures of viral load or clinical symptom scores (80). In the RCT, phase 3, BLAZE-1 trial, including 1035 outpatients with mild or moderate COVID-19, at high risk for progressing to severe COVID-19 (including 6.4% of immunosuppressed patients) 2.1% patients in the bamlanivimab 2800 mg + etesevimab 2800 mg group had a hospitalization or died by Day 29 versus 7.0% in the placebo group (relative risk difference, 70%; P<0.001, NNT=20.4) (81). No deaths occurred in the bamlanivimab–etesevimab group compared to 10 deaths in the placebo group. According to the unpublished results of the BLAZE-4 phase 2 trial, the only authorized dose of bamlanivimab is 700 mg combined with etesevimab 1400 mg (link). In the US, on June 25, 2021, the distribution of bamlanivimab plus etesevimab was temporarily paused as virologically resistant variants Gamma (P.1) and Beta (B.1.351) constituted >5% of samples identified through genomic surveillance (link). On the 2nd of November 2021, EMA ended the rolling review of bamlanivimab and etesevimab after Eli Lilly decided to withdraw from the process.

Data on Omicron variant indicate that it escapes neutralization by bamlanivimab+etesevimab (82).

1.4.4 Casirivimab + imdevimab (Ronapreve, REGEN-COV)

Ronapreve® (REGEN-COV, REGN-CoV2 or REGEN-CoV2) consists of two antibodies that bind to different regions of the SARS-CoV-2 spike protein receptor. This cocktail of mAbs is no longer available in Belgium and is not recommended for Omicron variants.

Available evidence in the hospital setting:

Treatment of hospitalized patients with severe COVID-19:

In the RECOVERY, RCT, open-label trial, REGEN-COV (casirivimab 4g and imdevimab 4g, IV) plus standard of care (including corticosteroids) was compared with standard of care alone, in hospitalized COVID-19 patients. 3153 patients (32%) were seronegative for SARS-CoV-2, 5272 (54%) seropositive and 1360 (14%) with unknown status at baseline. In the seronegative group, 396 (24%) in the REGEN-COV group and 451 (30%) of standard of care died within 28 days (rate ratio 0.79 95% CI 0.69-0.91; p=0.0009 NNT: 16.7). The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (p-value for heterogeneity = 0.001). The authors conclude that REGN-COV, in hospitalized patients with severe COVID-19, should only be used in SARS-CoV-2 seronegative patients. This is the first study to have shown efficacy of mAbs in hospitalized patients with COVID-19 (83).
Available evidence in the ambulatory setting:

Treatment of mild or moderate COVID-19 outpatients:
In an interim analysis of a phase 2-3 trial studying the effect of a combination regimen of casirivimab and imdevimab (NCT04425629) in 275 outpatients, a significant decline in viral load on day 7 was observed when compared to placebo, especially in seronegative patients and in patients with high viral load (84). However, the impact on clinical outcomes (medically attended visit) were less clear.

In the phase 3 portion of this same study in high-risk outpatients who received various doses of REGEN-COV (2400mg vs 1200mg vs placebo), the results showed that both REGEN-COV dosage regimens significantly reduced hospitalization or death by day 29 (respectively 71.3% reduction; p=0.001[18/1355, 1.3% vs 62/1341, 4.6%; NNT 90.3], and 70.4%; p=0.002 [7/736, 1.0% vs 24/748, 3.2%; NNT=45.45]) [48]. Efficacy of REGEN-COV (hospitalization or death, resolution of symptoms and viral load reduction) was consistent across subgroups, including patients that were SARS-CoV-2 seropositive at baseline. Based on that study, (85), the FDA modified the dosage to casirivimab 600mg plus imdevimab 600mg (June 2021). The same dosage is approved by the MHRA (The UK Medicines and Healthcare products Regulatory Agency and since the 12th of November by the EMA (link). Subcutaneous injection can be given when IV administration is not feasible or would lead to treatment delay (link).

Post-exposure prophylaxis:
The results of a phase 3 trial (part A) on subcutaneous REGEN-COV prophylaxis among uninfected (PCR negative) household contacts exposed to SARS-CoV-2 at home showed 81.4% risk reduction of a symptomatic infection compared with placebo (11/753 [1.5%] vs. 59/752 [7.8%], number needed to treat [NNT]: 15.9) and a shorter time to resolution of symptoms (1.2 vs. 3.2 weeks). One third of the subjects (30.5%) had at least one risk factor for severe COVID-19. The main risk factors included: BMI ≥ 35 kg/m2 (13.7%), age ≥ 65 years (8.7%), and diabetes (6.8%). Very few immunosuppressed patients were included in the study (1.5%) (86). In Part B of the same study, which compared REGEN-COV SC to placebo for preventing the progression of early SARS-CoV-2 infection in asymptomatic close contacts (PCR SARS-CoV-2 positive, primary analysis focused on seronegative participants), a 31.5% relative risk reduction of developing symptomatic infection in the REGN-COV group (29/100 [29.0%] vs 44/104 [42.3%]; p=0.038), was observed (87).

The eight-month post hoc analysis of the part A study shows that a single SC administration of casirivimab + imdevimab prevents symptomatic infections up to 5 months after injection. Patients could be vaccinated after the first 28 days of follow-up and the numbers of vaccinated patients were balanced in both groups (about 35%). It should be noted that the study started on 13 July 2020 and ended on 4 October 2021, before the emergence of the Omicron lineage variants (Delta period). Therefore, the results of this study cannot be transposed to the current epidemiological situation, for which the use of Ronapreve is contraindicated (88).

On the 12th of November 2021, the EMA gave a marketing authorisation for Ronapreve (casirivimab / imdevimab) to prevent and treat COVID-19 (within 7 days of symptom onset) in adults and adolescents as of age 12, ≥40 kg, who do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19. The dosage regimen for treatment and post-exposure prophylaxis is a single 600-600mg iv infusion or sc injection. For pre-exposure prophylaxis, dosage regimen is initially a 600-600mg infusion/injection followed by 300-300mg infusion/injection every 4 weeks (no data on repeat dosing beyond 24w). This mAbs cocktail is no longer recommended in Belgium.

1.4.5 Regdanvimab

Available evidence in the hospital setting
No data.

Available evidence in the ambulatory setting
A phase 2-3 trial of 325 adult outpatients with COVID-19 (study CT-P59, unpublished) showed a smaller proportion of severe COVID-19 (hospitalization, oxygen requirement or death) by day 28 of 4.4% when analysing pooled dosage regimens of CT-P59 (40mg/kg and 80mg/kg) versus 8.7% in the placebo group (link).

A main study involving 1,315 patients with COVID-19 showed that Regkirona led to fewer patients requiring hospitalisation or oxygen therapy, or death, when compared with placebo. Among the patients at increased risk of developing severe illness, 3.1% of patients treated with Regkirona (14 out 446) were hospitalised, required supplemental oxygen or died within 28 days of treatment compared with 11.1% of patients on placebo.
The majority of patients in the study were infected with the original SARS-CoV-2 virus or the Alpha variant; data on the efficacy of Regkirona against new circulating SARS-CoV-2 variants is currently limited.

On the 12th of November 2021, EMA gave a marketing authorisation for Regkirona (regdanvimab, CT-P59) for treating adult patients with COVID-19 who do not require supplemental oxygen and are at increased risk for progression to severe COVID-19. The posology is one single iv infusion 40mg/kg.

A present, there is no availability of this product in Belgium.

1.4.6 Sotrovimab

Main message
Sotrovimab is no longer recommended and is no longer available in the strategic stock.

Available evidence in the hospital setting
In a multinational, randomised, placebo-controlled clinical trial (NCT04501978), 546 hospitalised COVID-19 patients with symptom onset of up to 12 days received either sotrovimab 500 mg IV (n=184), or BRII-196 1000 mg plus BRII-198 1000 mg IV - Brii Biosciences (n=183) or placebo (n=179), in addition to standard care (including remdesivir). Patients were excluded if they required high flow oxygen therapy. The enrolment was halted on the basis of the interim futility analysis. Neither sotrovimab or BRII-196 plus BRII-198 showed efficacy for improving clinical outcomes (ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group) (89).

Available evidence in the ambulatory setting
The phase 3 COMET-ICE trial (NCT04545060), evaluating a single 500 mg infusion of sotrovimab compared to placebo in 1057 high-risk outpatients (most common risk factors: obesity: 63%, >55 years: 46% and diabetes: 23%) demonstrated an 79 % (p< 0.001) reduction in hospitalization or death at day 29 in the sotrovimab group vs. placebo (1% vs 6% NNT:20) (90).

On the 16th of December 2021, the EMA issued a positive opinion on Xevudy®, thus resulting in a grant for marketing authorization for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age of weighing at least 40 kg) (link).

Given the current circulating variants and conflicting in-vitro data on the neutralising efficacy on these variants (71–73), the administration of Sotrovimab is not recommended. WHO reviewed the evidence on sotrovimab and casirivimab-imdevimab, and maintains strong recommendations against their use for treating COVID-19, stating these monoclonal antibodies lack or have diminished activity against the current circulating virus variants (https://www.emro.who.int/media/news/information-note-on-new-covid-19-omicron-subvariant-xbb15.html).

1.4.7 Tixagevimab and cilgavimab (AZD7442)

AZD7442 is a combination of two fully human, long-acting SARS-CoV-2-neutralizing antibodies, AZD8895 (tixagevimab) and AZD1061 (cilgavimab). The half-life extension more than triples the durability of its action compared to conventional mAbs (91). Tixagevimab/cilgavimab (EVUSHELD®) was authorized for marketing in Europe in March 2022 for prophylactic use, and then in September 2022 for therapeutic use.

Available evidence in the hospital setting
The AZD7442 combination was studied in a randomized, double-blind, phase 3 placebo-controlled trial by the ACTV-3 TICO study group in hospitalized patients with COVID-19 in the USA, Europe, Uganda, and Singapore (NCT04501978). Patients received either the AZD7442 combination intravenously in addition to remdesivir or a placebo in addition to remdesivir. Patients with an acute organ failure were excluded from the trial. The primary outcome was sustained recovery up to day 90, defined as remaining 14 consecutive days at home after hospital discharge. 1455 patients participated in the trial. The sustained recovery was not significantly different between groups in the full cohort, nor in the seronegative subgroup: 89% for the AZD7442 combination group vs. 86% for the placebo group. This translated into a recovery rate ratio (RRR) of 1.08 (95% CI 0.97-1.20); p=0.21. However, mortality was lower in the AZD7442 combination group compared to placebo: 61 (9%) vs. 86 (12%); HR: 0.70 (95% CI 0.50-0.97); p=0.32) (92).

The AZD7442 combination has been evaluated in hospitalized patients with COVID-19 in the DisCoVeRy trial (NCT04315948).
Available evidence in the ambulatory setting

In the phase III PROVENT pre-exposure prophylaxis trial (NCT04625725), 5197 unvaccinated, SARS-CoV-2-negative adult patients who were expected to have an inadequate response to vaccination (but <4% of immunocompromised included) or an increased risk of exposure, were randomized to receive intramuscular AZD7442 (150 mg tixagevimab +150 mg cilgavimab, 3460 patients) or placebo (1737 patients). The study period was between November 2020 and March 2021. The primary efficacy end point was symptomatic COVID-19 at day 183 and occurred in 8/3441 (0.2%) in the AZD7442 group and 17/1731 participants (1.0%) in the placebo group (relative risk reduction, 76.7%; 95% CI, 46.0 to 90.0; P<0.001). Five critical COVID-19 cases and 2 deaths occurred in the placebo group. One death due to myocardial infarction occurred in the AZD7442 group (<0.1%), and thus requires vigilance in patients with cardiovascular disease (93).

The TACKLE study is a phase 3 RCT including 910 non-hospitalised, unvaccinated patients with mild to moderate COVID-19 (456 in the tixagevimab-ciligavimab 600mg IM and 454 in the placebo group). The mean age of the participants was 46.1 years. Only 5% were immunocompromised. At Day 29, 18/407 (4%) of patients in the tixagevimab-ciligavimab group versus 37/415 (9%) of 415 in the placebo group progressed to severe disease or death (relative risk reduction 50.5% [95% CI 14.6-71.3]; p=0.0096, NNT=20). Three COVID-19-related deaths occurred in the tixagevimab-ciligavimab group, and six in the placebo group. There was no difference in adverse events between the 2 groups. Note that this study was conducted before the Omicron era (94). Two US RCT, (Phase 2) for early mild/moderate COVID-19 outpatients (February to May 2021, prior to Delta and Omicron variants, predominantly unvaccinated patients) treated by tixagevimab-ciligavimab 300 mg IV (n=58, high-risk patient) or 600 mg IM (n=106, low and high risk patients), or a placebo (n=117+56) showed no significant differences in symptom improvement time between tixagevimab-ciligavimab and placebo, regardless of the administration method (95).

The EMA started the rolling review of Evusheld® (tixagevimab and cilgavimab) on 14 October 2021. On the 24th of March 2022, EMA recommended granting a marketing authorization for Evusheld® for the prevention of COVID-19 in adults and adolescents from 12 years of age, weighing at least 40kg before potential exposure to the SARS-CoV-2 virus (link). On the 26th of September 2022, EMA recommended to grant marketing authorization of Evusheld® for the treatment of COVID-19 in adults and adolescents from 12 years of age, weighing at least 40kg, at risk of progressing to severe COVID-19, and not requiring supplemental oxygen (link). On December 9, 2022, the EMA Emergency Task Force (ETF) warned that currently approved monoclonal antibodies for COVID-19 are unlikely to be effective against emerging SARS-CoV-2 strains (link).

The therapeutic dosage of EVUSHELD® is 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections.

A higher proportion of subjects who received EVUSHELD® had serious adverse events of myocardial infarction and heart failure. All subjects had cardiac risk factors and/or a history of cardiovascular disease, and there was no clear temporal pattern (link).

Several of the currently circulating variants were not yet circulating during the period of the initial tixagevimab-ciligavimab clinical trials.

Although vaccination prevents severe disease and mortality in a large majority of patients, breakthrough infections have been reported (link). The final decision on mAbs treatment should integrate the clinical opinion of the prescribing (hospital-based) physician and a multidisciplinary expert panel, consisting of at least an infectious disease physician.

Viral genomic monitoring during mAbs therapy is suggested to monitor the risk of developing resistance during treatment. Patients treated with mAbs should be under quarantine and a SARS-CoV-2 nasopharyngeal PCR test should be performed 7-10 days after treatment. If the test is positive, virus sequencing should be performed. SARS-CoV-2 variant classifications and definitions are available via the CDC.

Current recommendations

The workgroup no longer recommends administration of EVUSHELD® to treat COVID-19 in immunocompromised patients, unless evidence for an infection with a susceptible variant can be demonstrated (conditional recommendation based on low quality evidence).
1.5 Convalescent plasma

Available evidence in the hospital setting

Animal studies with SARS-CoV-1 and SARS-CoV-2 infections indicate a protective role of neutralizing antibodies. In addition to marked antiviral activity, plasma administration has been associated with decreased inflammatory markers in a trial in India (96). Several observational studies, non-controlled and controlled non-randomized trials, RCT’s, and several meta-analyses and living reviews have been published (97,98). Several observational studies show survival benefit of transfusing COVID-19 convalescent plasma (CPP) with high antibody titers (99). In contrast, RCT’s could not demonstrate a benefit on mortality of CPP in hospitalized patients with COVID-19, among which the RECOVERY trial is the largest one published until now (100–106). The RECOVERY trial randomized 11,558 patients to convalescent plasma or usual care. They did not find any difference in 28-day mortality between the two groups (both 24%). There was also no difference in secondary outcomes such as discharge at day 28 or progression to mechanical ventilation or death in those not mechanically ventilated at randomization (107). The REMAP-CAP study, carried out in critically ill patients also halted recruitment in the convalescent arm due to futility (108). A Cochrane review including some unpublished data (including those from the RECOVERY trial at that time), and a meta-analysis performed by the RECOVERY group, did not find a difference in mortality between convalescent plasma and usual care (105–110). Review of all 29 available RCTs in moderate to severe disease up to the 3rd of March 2023 reviewed by the Cochrane haematology group confirms that CPP has no benefits in these patients (116).

In a Belgian open-label trial among 475 patients with COVID-19-induced ARDS and invasive mechanical ventilation for less than 5 days, the administration of CPP with a neutralizing antibody titer of at least 1:160 led to a significantly reduced mortality. At day 28, mortality was 35.4% in the convalescent-plasma group and 45.0% in the standard-care group (P = 0.03). This effect was observed mainly in patients who underwent randomization 48 hours or less after the initiation of invasive mechanical ventilation (117).

It remains unclear if certain patient groups, in particular patients with severe immunodepression might benefit from CPP. Some underpowered RCTs and subgroup analysis of the REMAP-CAP might hint in that direction, but evidence remains to scarce to advice for or against its use (118,119).

Available evidence in the ambulatory setting

An Argentinian blinded RCT evaluated early (i.e. within 3d of symptom onset) administration of convalescent plasma in older COVID-19 patients, i.e. >75y or >64 -75y with comorbidities (120). They found a RR reduction of 0.52 (95% CI 0.29-0.94). The study was terminated early due to a fall in the COVID-19 incidence in Argentina, including 76% percent of the previewed inclusion number. On the other hand, the NIH trial C3PO evaluating convalescent plasma compared to standard of care for treatment of early-onset (<7 days), non-hospitalized COVID-19 patients (≥50 years old or with a risk factor) was halted after interim analysis of 511 participants (of the 900 planned) found no difference in disease progression between the two groups (121). The same results were found in pooled data from the Conv-ert, (Spain), and CoV-Early (The Netherlands), double blind randomized placebo-controlled trials in ambulatory COVID19 patients (n= 797; ≥ 50y with symptom onset ≤ 7d) (122). Sullivan et al, on the other hand, included 1225 patients in a double-blind placebo (plasma) controlled randomized trial, and found an absolute risk reduction for hospitalization within 28d of 3.4% (2.9% in CPP treated vs 6.3% in placebo treated) (123). The differences found between previous studies might have several explanations: patient population included, time of plasma infusion, type of placebo. A recent Cochrane review, including the aforementioned studies thus concluded that the level of of evidence for mild COVID 19 remains moderate for hospital admission or death at 28 days(116). It is important to note that most studies were run before the current omicron variant and high vaccination uptake, and the group of immunocompromised patients who might benefit from CPP was underrepresented in the currently published studies.

Notes on treatment with convalescent plasma

Administration of CCP could be considered in case of persistent viral shedding (> 1 month) in severe COVID-19 patients with B cell-related immunosuppression (including patients on Rituximab and other B-cell depleting agents) unable to mount an antibody response, as shown in several case reports, case series and a retrospective case-control studies (124–128). In the REMAP-CAP a trend towards a lower amount of organ support free days was seen in the subgroup of the immunocompromised. Furthermore, the amount of CPP, neutralizing antibody needed, is still a matter of debate. A small, well-conducted, but underpowered RCT (due to early termination of the study), using hyperimmune IVIG in immunocompromised patients suggests a
beneficial effect of high dose antibody therapy (122). This together with the experience of the beneficial effect of monoclonal antibodies suggests that higher titers or dosed CPP might be necessary (130).

Furthermore, emergence of viral populations with significant mutations in the spike protein has been reported during treatment of immunocompromised patients with convalescent plasma (131).

Reduced in-vitro neutralization to the current Omicron variant has been shown when testing convalescent plasma from previously circulating SARS-Cov2 variants (132). Formal studies evaluating the value of convalescent plasma in this setting are needed (133,134).

1.6 Intravenous immunoglobulines (IVIG)

Main message
At this moment there is no place for IVIG or hyperimmune IVIG (hIVIG) as standard treatment for severe COVID-19. Further studies are awaited to confirm a possible interest of commercial IVIG preparations among immunocompromised hypogammaglobulinemic patients presenting with protracted COVID-19. For its place in the treatment of COVID complications, like multisystem inflammatory syndrome, we refer to current international guidelines.

Available evidence in the hospital setting:
Early in the pandemic, several small trials reviewed in a meta-analysis, showed promising results of IVIG treatment in severe COVID, low level of certainty (135). An additional double-blind, placebo-controlled, RCT in patients with COVID 19 ARDS could not find an effect on ventilator free days at 28d. This study had several limitations; particularly, the study was probably underpowered due to the small effect measured (136).

Studies on hyperimmune/concentrated immunoglobulin preparations are scarce, a pilot phase I/II study in severe COVID showed that it was safe and a non-significant positive effect on survival (137). A more recent, international, multi-centric, double-blind, placebo-controlled, phase 3, randomised trial in 593 hospitalized patients also failed to show efficacy on day 7 (based on a 7-category ordinal endpoint) (138). A small well-conducted but underpowered RCT, due to early termination of the study, using hIVIG in immunocompromised patients with acute hypoxemic COVID-19 suggests a beneficial effect of high dose antibody therapy (139), as compared to IVIG. A study reported that most IVIG solutions commercially available in the UK from mid to late 2022 contained neutralising anti-SARS-CoV-2 antibodies. When administered at standard replacement dose (0.4-0.6g/kg), IVIG induced increases in pseudo-virus neutralization titers close to levels of healthy controls. The authors also report that the administration of IVIG at replacement doses of 0.5 g/kg, generally as repeated dose over two days and then every 4 weeks, in combination with remdesivir, induced viral clearance in all of 9 immunocompromised hypoglobulinemic patients that were treated. All but one of those treated patients presented a chronic and relapsing course with a median duration of disease of 189 days. Further studies are required to confirm the efficacy of this strategy (140).

Available evidence in the ambulatory setting
No data.

1.7 Janus kinase inhibitors

Main message
Baricitinib (and other Janus kinase inhibitors) are anti-inflammatory drugs targeting multiple cytokines that have shown a survival benefit when administered in addition to standard of care (i.e. systemic corticosteroids). The EMA is currently reviewing baricitinib as a possible COVID-19 treatment. NIH recommends baricitinib in addition to dexamethasone in severe patients as an alternative to tocilizumab. Tofacitinib is also proposed as an alternative to baricitinib when unavailable (link).

1.7.1 Baricitinib

Available evidence in the hospital setting
Baricitinib is an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2. In a randomized placebo-controlled trial in patients with moderate and severe COVID-19, treatment with baricitinib 4mg and remdesivir was shown to reduce recovery time and to accelerate improvement in clinical status when compared to RDV alone (141). Corticosteroids were not considered standard of care in this study, so the comparison of baricitinib versus baricitinib in association with corticoids was not evaluated. Prices of baricitinib and RDV are significantly
higher than steroids, so this treatment should not be used as standard of care pending further evaluation: including use without RDV, use on top of steroids or use in comparison with steroids. One large double blind randomized placebo-controlled trial (SOC included systemic corticosteroids in 80% of patients) showed no influence of baricitinib on combined primary endpoints (progression to requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death by day 28), but there was a significant reduction of mortality at day 28 (hazard ratio [HR] 0.57 [95% CI 0.41–0.78]; nominal p=0.0018) and day 60 (HR 0.62 [95% CI 0.47–0.83]; \( p=0.0050 \)) (142). In an addendum cohort of critically ill patients (baseline IMV/ECM, with 86% corticosteroid treated), the COV-BARRIER study demonstrated a reduction in 28-day all-cause mortality compared to placebo (39.2% vs 58.0%; hazard ratio [HR]=0.54 [95% CI 0.31–0.96]; \( p=0.030 \)). This reduction persisted through day 60 (mortality 45.1% vs 62.0%; HR=0.56 [95%CI 0.33–0.97]; \( p=0.027 \)) (143). Preliminary results (pre-print) of the baricitinib arm in the RECOVER trial have become available (144). A Cochrane meta-analysis included those four trials (10,815 participants), together with one trial of tofacitinib (289 participants) and one trial of ruxolitinib (41 participants). It showed that JAK inhibitors probably decrease all-cause mortality at up to day 28 (95/1000 participants in the intervention group versus 131/1000 participants in the control group; 6 studies, 11,145 participants; risk ratio (RR) 0.72, 95% confidence interval (CI) 0.57 to 0.91; moderate-certainty evidence), and decreased all-cause mortality at up to day 60 (125/1000 participants versus 181/1000 participants; RR 0.69, 95% CI 0.56 to 0.86; 2 studies, 1628 participants; high-certainty evidence) (145). The results from the Barriers trial, a randomised, double-blind, placebo-controlled phase 3 trial, that evaluated the efficacy and safety of baricitinib in hospitalized vaccinated and non-vaccinated adults with severe or critical COVID-19 were published. Only 284 patients of the planned 1900 participants were randomized due to premature termination of the trial due to external evidence. Nevertheless, a key finding of the trial, based on post-hoc analysis, was a possible safety signal in vaccinated compared to unvaccinated participants; more serious adverse events, including more respiratory complications, severe infections, and deaths at 60-days were observed in the vaccinated patients who were older and had more comorbidities than the unvaccinated patients. Further investigations are warranted in vaccinated patients (146).

The TACTIC-R is a phase 4 randomised, open-label platform trial that was undertaken in the UK. 417 participants were recruited and randomly assigned to standard of care alone (145 patients), baricitinib (137 patients), or ruxolizumab (135 patients). Neither baricitinib nor ruxolizumab was effective in reducing disease severity in patients selected for severe COVID-19, and the trial was stopped after the primary interim analysis on grounds of futility. Safety was similar between treatments and standard of care (147).

On the 29th of April, the EMA began the evaluation of an application to extend the use of Olumiant (baricitinib) to include treatment of COVID-19 in hospitalized patients from 10 years of age who require supplemental oxygen. However, the company retracted the application. Nevertheless, the living WHO guideline has given a strong recommendation since September 2022 to administer baricitinib as an alternative to IL-6 receptor blockers in combination with corticosteroids to patients with severe or critical COVID-19 (148).

### Available evidence in the ambulatory setting

No data.

1.7.2  **Tofacitinib**

### Available evidence in the hospital setting

Tofacitinib is an oral JAK-inhibitor approved for the treatment of rheumatologic diseases and ulcerative colitis (Xeljanz®). A RCT evaluated the effects of tofacitinib (10 mg q12h for up to 14 days) in hospitalized COVID-19 patients not requiring ventilation (within 72 hours of admission) in comparison to placebo. This treatment led to a significant reduction in the incidence of death or respiratory failure (18.1% vs 29.0%, risk ratio 0.63, \( P=0.04 \)); this effect was consistent across the different levels of oxygen requirements at baseline. One limitation of the study is its relatively limited sample size (\( n=289 \)); also, corticosteroid use was high in both groups (78.5%), while other immunomodulatory treatments were not allowed. The study showed no increased risk of secondary infections associated with the use of tofacitinib. Importantly, patients with a history of or current thrombosis, personal or first-degree family history of blood clotting disorders, immunosuppression, any active cancer, or those with some cytopenias were excluded from this trial. A reduced dose of 5mg twice daily was administered in patients with reduced glomerular filtration rate (<50mL/minute), in those with moderate liver dysfunction and in those with a strong CYP3A4 inhibitor or a combination of a moderate CYP3A4 inhibitor and a strong CYP2C19 inhibitor (149). Nevertheless, the WHO living guideline has given a weak recommendation against its use in patients with severe or critical COVID-19, outside of clinical trials due to low certainty of evidence (148).
Available evidence in the ambulatory setting

No data.

1.7.3 Ruxolitinib

Only preliminary data are available for ruxolitinib; the data is not sufficient to support its use outside of studies (150).

1.8 Interferon

Main message

Interferons (IFN) have antiviral effects and modulate the immune response (151). At this moment there is insufficient evidence to support the use of interferon treatment in early or severe COVID-19 disease, although one study showed promising results regarding treatment with pegylated interferon lambda in preventing hospitalization in outpatients.

Available evidence in the hospital setting

There are several case series, case-control trials, small RCT’s and the interim results of the WHO-solidarity trial that have been published so far. Hung et al compared combination therapy including IFN β-1b, ribavirin and lopinavir/ritonavir (n=86) vs lopinavir/ritonavir alone (n= 41) in an open label RCT (152). Only 52 patients starting therapy <7d of symptom onset received at least one dose of interferon, as by study protocol. They found a shortened viral shedding and faster clinical improvement in the IFN-containing arm. Another RCT evaluated IFN β-1b with or without standard of care including hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir (both groups n=33). They found a faster clinical improvement, in primary outcome; and a decreased ICU admission, although the study was probably underpowered for this (153). The same group also evaluated IFN β-1a in addition to the same standard of care (n=42) vs standard of care alone (n=39), and could not find any difference in clinical response (154). Decreased mortality was found in the IFN group. This study has several limitations: >30% of patients had no laboratory-confirmed infection, a very high mortality was observed in the control group and a large drop-out was seen in each study group. Furthermore, IFN therapy was associated with more adverse events. Results from the WHO-SOLIDARITY trial show that Interferon IFN β-1a given with or without lopinavir/ritonavir, respectively 1412 and 651 patients, did not provide any survival benefit vs control in hospitalized patients (HR 1.16 (0.96-1.39)) (42). The results of the DisCoVeRy trial have been published, including a lopinavir/ritonavir interferon β-1a arm (155). There was no impact on clinical outcomes. Inclusion in the study arm was stopped prematurely due to futility.

Several smaller RCTs have looked at IFN β-1a, in addition to SOC including lopinavir/ritonavir, in severe COVID-19 and could not find a clinical benefit (154,156,157). An Indian multicenter open label RCT evaluated a single dose of Pegylated interferon α2b in moderate COVID-19 with only modest clinical improvement and viral clearance (158). Little added value was shown when adding interferon β-1b to RDV either (159,160).

One small, underpowered RCT looked at the effect of combination of inhaled interferon β-1b and Favipiravir vs standard of care with hydroxychloroquine in severe COVID-19, finding no effect (161). Another pilot double-blind placebo RCT found that hospitalized COVID-19 patients treated with 14 days of nebulized interferon β-1a had a greater odds for clinical improvement (162). The double-blind placebo-controlled Sprinter II-trial could not confirm these earlier findings; no effect on time to recovery and hospital discharge was shown(163). This could be explained by the improved standard of care and increased vaccination status.

Available evidence in the ambulatory setting

Two small studies have looked at the effect of early single dose administration of peginterferon-lambda on viral clearance in outpatients with COVID-19 and found opposing results (164,165). A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions (166,167). As part of the TOGETHER platform trial, the efficacy of a single dose of pegylated interferon lambda (subcutaneous injection) in preventing hospitalization or an emergency department visit (observation for >6 hours) due to Covid-19 was evaluated in outpatients. 933 patients were assigned to receive pegylated interferon lambda and 1033 patients received placebo (825 saline placebo injection, others PO) between June 2021 and February 2022, during which several covid strains were active. Patients were predominantly vaccinated, with a median age of 43 years old and with and at least one high-risk criterion for progression of Covid-19. A total of 25 of 931 patients (2.7%) in the interferon group had a primary (composite) outcome event, as compared with 57 of 1018 (5.6%) in the placebo group, a difference of 51% (RR 0.49; CI 0.30-0.76; NNT=66). The effects were consistent across dominant variants and independent of vaccination status. The
relative risk for death or hospitalization due to Covid-19 was 0.61 (CI 0.36-0.99). When analysis was restricted to treatment within 3 days after the onset of symptoms, larger treatment effects were observed. This first phase-3 trial on pegylated interferon lambda shows it has potential in preventing clinical events among outpatients with Covid-19 (168).

Further studies are needed to clarify the role of Interferons in the treatment of COVID-19.

1.9 Chloroquine and hydroxychloroquine

As there is significant evidence to support that this treatment is not recommended, the follow-up of this evidence is no longer a priority and might no longer be up to date.

Main message

Current high-quality evidence demonstrates that hydroxychloroquine (HCQ) does not improve clinical outcomes among COVID-19 infected patients. It has been decided since the beginning of June 2020 (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore. In December 2020, the WHO recommended against the use of (hydroxy-)chloroquine in clinical care regardless of COVID-19 severity.

Available evidence in the hospital setting

Chloroquine and hydroxychloroquine initially appeared promising because it could inhibit replication of SARS-CoV-2 in vitro (169).

The role of hydroxychloroquine for treatment of hospitalized COVID-19 patients was assessed in the RECOVERY, SOLIDARITY and DisCoVeRy trials. None of these studies found improved clinical outcomes among treated patients. The prospective RCT RECOVERY in UK stopped enrolling patients on the 5th of June after finding no beneficial effect of high dose hydroxychloroquine (9600 mg in total over 10 days) in patients hospitalized with COVID-19. For the same reason (absence of efficacy in hospitalized patients), the SOLIDARITY trial communicated the suspension of recruitment in the HCQ arm (9600 mg over 10 days) on the 18th of June (link). Similarly, the DisCoVeRy trial stopped enrolling participants in the HCQ arm (5600 mg in total over 10 days) at the same period. The results of the large RECOVERY trial on HCQ efficacy in hospitalized COVID-19 patients have shown that mortality at Day 28 was similar in HCQ recipients compared to standard of care (421/1561, 27% versus 790/3155, 25%; p=0.15). No benefit was observed for all secondary outcomes and subgroups of patients (170). Another smaller RCT in Brazil conducted in mild-to-moderate hospitalized patients did not find any improvement in the clinical status (seven-level ordinal scale) of participants who received HCQ (total dosage: 5600 mg), alone or with azithromycin (500 mg/day for 7 days) (171).

Available evidence in the ambulatory setting

The role of hydroxychloroquine as post-exposure prophylaxis or as early treatment for mild COVID-19 disease was also assessed through additional RCTs, yet no clinical benefit was found. One RCT using HCQ (low-dose) as post-exposure prophylaxis (PEP), showed no prevention of “illness compatible with COVID-19” [40]. This trial had however several limitations such as undocumented treatment adherence and no laboratory confirmation of SARS-CoV-2 infections in 85% of the participants. Another RCT by the same group studied early administration of HCQ in mild/ambulatory patients with laboratory-confirmed or symptomatic contacts (n=423), and no substantial symptom reduction was observed in the HCQ arm compared to masked placebo (172). Here again, many participants (about 40%) were not tested for SARS-CoV2 infection. In a well-designed Spanish RCT evaluating early treatment with HCQ in adults with mild disease (n=293), no clinical (shortening of symptoms) nor viral (reduction of shedding) benefits were observed (173). A cluster-randomized trial by the same Spanish group did not show any reduction in the incidence of SARS-CoV-2 infection nor symptomatic COVID-19 when HCQ was used in post-exposure prophylaxis in healthy persons exposed to a PCR-positive case patient (174).
1.10 Lopinavir/ritonavir

As there is significant evidence to support that this treatment is not recommended, the follow-up of this evidence is no longer a priority and might no longer be up to date.

Main message
Due to lack of evidence for clinical benefit in the SOLIDARITY, RECOVERY and DisCoVeRy trials, lopinavir/ritonavir (LPV/r) is not recommended as a treatment in COVID-19 disease. In December 2020, WHO recommended against the use of LPV/r in clinical care regardless of COVID-19 severity.

Available evidence in the hospital setting
In an RCT, lopinavir/ritonavir (LPV/r 400 mg/100 mg twice daily), initiated more than 12 days after symptom onset (median, IQR 11–17 days), did not show significant clinical benefits in hospitalized patients with COVID-19 (175). Another small RCT conducted in China did not show any viral or clinical benefit either (or at best very marginal) (175). On the 4th of July 2020, the WHO announced that the lopinavir/ritonavir arm was discontinued in the SOLIDARITY trial because of lack of benefit (link). This arm was also stopped in RECOVERY and DisCoVeRy for the same reason. Finally, a benefit risk-assessment performed by the BRAT (Benefit-Risk Action Team) network and published on the 23rd of June 2020, concluded that the benefit-risk profile for lopinavir/ritonavir in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available (176). The results of the large RECOVERY trial in hospitalized patients with COVID-19 confirmed that lopinavir/ritonavir had no beneficial effect on mortality at day 28 (374/1616, 23% versus 767/3424, 22%, p=0.60) nor on any secondary endpoint (duration of hospital stay, progression of disease) (177). Results from ongoing clinical trials are still awaited.

Available evidence in the ambulatory setting
No data.

1.11 Favipiravir

Main message
Although some encouraging pre-clinical data (mainly in hamster models) have been published, there is currently no evidence from clinical trials concerning the potential utility of this drug for in- or out-patients with COVID-19 infection. This drug is currently unavailable for treatment outside of clinical trials in Belgium.

Available evidence
Favipiravir has a half-cytotoxic concentration (CC50) > 400 μM and the EC50 of favipiravir against SARS-CoV-2 in Vero E6 cells was 61.88 μM/L (much higher than the EC50 of favipiravir for influenza), resulting in a selectivity index (SI) > 6.46 (178). The half-life is approximately 5 hours. Therefore, higher dosing ranges are considered necessary for the treatment of COVID-19 than for influenza (loading dose of 2400mg to 3000mg BID followed by a maintenance dose 1200mg to 1800mg BID) (179). An antiviral effect has been observed in animal models (hamsters) at high dosage (180). This observation has been confirmed in another experiment in Syrian hamsters (181). The combination of favipiravir with molnupiravir (see below) demonstrated a synergetic benefit in the hamster infection model (168).

Available evidence in the hospital setting
An interim analysis of a small phase 2 RCT showed a lower rate of PCR positivity at day 5 post-favipiravir initiation but with no difference at day 10 (183). Another small RCT in India in mild/moderate patients did not find any significant effect on the duration of viral shedding compared to placebo (but a slight reduction in time to clinical cure) (184). A multicentric RCT in Iran did not show any clinical benefit in hospitalized COVID-19 patients treated with favipiravir when compared to LPV/r (185). Also, early administration of favipiravir (1800 mg BID D1 and 800 mg BID till D5) was not associated with any clinical benefit in a large RCT (n=500) among high-risk mild/moderate Malaysian hospitalized patients (186).

Available evidence in the ambulatory setting
In a small RCT conducted between December 2020 and March 2021 in three outpatient centers in Iran, favipiravir showed no benefit in preventing the hospitalization of mild to moderate COVID-19 patients. Limitations of this study include its small sample size and noncompliance of participants (187).
1.12 Molnupiravir (Lagevrio®)

Main message
This drug has not been shown to be clinically effective in large, real world RCTs. This drug has not received the market authorization by EMA (February 2023). Molnupiravir is no longer recommended, and is no longer available in Belgium.

Available evidence in the hospital setting
The placebo-controlled, double-blind phase 2 trial (MOVE-IN) in hospitalized patients with confirmed COVID-19 and symptoms onset of 10 or fewer days evaluated different dosage regimens of molnupiravir compared to placebo: 200 mg, 400 mg or 800 mg of molnupiravir twice a day for five days in 304 participants (75 patients received placebo). Median time to recovery was 9 days in all groups, and recovery rates at day 29 were similar as well, ranging from 81.5% to 85.2%. None of the dosage regimens of molnupiravir demonstrated clinical benefit of sustained recovery (188). The Phase 3 trial (MOVE-IN) for hospitalized patients was therefore not initiated for possible futility. Preliminary phase 1 and phase 2 data suggest the drug is safe and has antiviral activity in humans as well. A phase 3 trial has been concluded (stopped before finishing recruitment, based on the recommendation of the independent Data Monitoring Committee, and in consultation with the U.S. Food and Drug Administration (FDA), due to positive results observed at the interim analysis) in which orally administered 800 mg molnupiravir bd vs placebo was given to non-hospitalized patients at risk of severe disease progression within 5 days of symptom onset (MOVE-OUT trial: NCT04575597). Updated results of the trial showed only a 30% relative risk reduction of hospitalisation and death through 30 days since treatment initiation among 1433 participants. There were 9 deaths in the placebo group and 1 in the group that received molnupiravir. Furthermore, in the pre-specified sub-group of patients with SARS-CoV2 nucleocapsid antibodies, low viral load, those with diabetes at baseline, several ethnic minorities such as Black, Asian and Native American, and patients enrolled in the Asia-Pacific region showed no positive effect with molnupiravir treatment, possibly due to small sample sizes (189). The PANORAMIC trial in the UK, comparing molnupiravir plus usual care to usual care alone in a randomized, controlled, open-label trial in adults with COVID-19 (<5 days of symptoms) at increased risk of adverse outcomes, also showed no reduction in hospitalisations or deaths. The trial included 25,783 participants (58.6% female) with a mean age of 56.6 years, 94.4% of whom had received at least 3 doses of vaccines against SARS-CoV2, where 103/12516 (0.8%) hospitalisations or deaths occurred in the molnupiravir group versus 96/12484 (0.8%) in the usual care alone group. However, recovery was faster 9 (5-23) days vs. 15 (7-not reached) days, and viral detection was reduced in the molnupiravir group compared to usual care (as 7/34 (21%) vs. 1/39 (3%), p= 0.039 were below detection level) (190).

1.13 Nirmatrelvir + Ritonavir (Paxlovid®)
PF-07321332 (nirmatrelvir) is a SARS-CoV-2 protease inhibitor, which blocks the activity of the SARS-CoV-2-3CL protease (Mpro) and has in-vitro pan-human coronavirus activity. Co-administration with ritonavir slows the metabolism of PF-07321332 (191).

Available evidence in the hospital setting
One randomized controlled trial has been published since the EPIC-HR trial, and this study could not demonstrate an effect of nirmatrelvir/ritonavir on mortality in hospitalized patients with Covid-19, but the study may have been underpowered to find a significant effect (192).

Available evidence in the ambulatory setting
The EPIC-HR trial is a randomised, double-blind study of non-hospitalised adults with COVID-19 who are at high risk of progression to severe disease. The study was stopped in November 2021 due to the demonstrated efficacy of Paxlovid® in the interim analysis. In the final analysis of the EPIC-HR trial, 5/697 (0.7%) of patients who received PAXLOVID within 3 days of symptoms onset were hospitalized up to day 28 post-randomization (hospitalized, 0 death), compared to 6.5% of patients who received placebo (44/682 hospitalised with 9 deaths), resulting in a risk reduction of 89% (p<0.0001). The incidence of adverse events was similar in both groups. Note that exclusion criteria in the study included the use of a drug that was highly dependent on CYP3A4 during treatment and for 4 days after the last dose of PF-07321332/ritonavir or the use of a potent CYP3A4-inducing drug (193).

The phase 2/3 study, EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients) evaluated Paxlovid in adults at standard risk and also includes vaccinated patients with acute symptomatic
COVID-19 infection (breakthrough infection) who have risk factors for severe disease. The EPIC-SR trial was terminated due to low incidence of the outcomes under study.

A third phase 2/3 study, EPIC-PEP (Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis) evaluated the efficacy of Paxlovid® in post-exposure after contact with a household member. The primary endpoint of reducing the risk of confirmed and symptomatic COVID-19 infection was not met.

On December 22, 2021, the FDA issued an EUA for (Paxlovid® for the treatment of adults and adolescent ≥12 years and ≥40 kg of age with mild to moderate COVID-19 and who are at high risk for progression to severe COVID-19, at the dosage (in patient with no renal impairment) of nirmatrelvir (300 mg) with ritonavir (100 mg) as soon as possible (within 5 days of the onset of COVID-19 symptoms) for 5 days (link).

Since 28 January 2022, Paxlovid® is authorized by EMA for treating COVID-19 high-risk adult patients with no need of supplemental oxygen. The treatment should be administered as soon as possible and within 5 days of symptoms onset (link).

A large number of observational studies on real-world effectiveness of nirmatrelvir/ritonavir in vaccinated populations and with Omicron as circulating variant have been published since its approval in January 2022 (194–206). A meta-analysis by KCE, including 32 studies published after October 2022, showed a significant protective effect of nirmatrelvir/ritonavir on outcomes such as mortality and hospitalization. The treatment effects are however smaller than witnessed in the EPIC-HR trial. Moreover, given the decreased incidence of severe outcomes of COVID-19 due to widespread vaccination, prior immunity through infection and circulation of less virulent variants, the number needed to treat (NNT) is presumably much higher in the current context than at the time of the EPIC-HR trial (which found an NNT of 18). An estimation of current NNT was also performed in the meta-analysis by looking at the incidence of the outcome under study in the five largest observational studies, and using the pooled estimate from the meta-analysis as the relative risk for the outcome of interest. The incidence of mortality or hospitalization varied from 0.51% to 4.51%, leading to an estimated NNT of 48 to 426 (207). The latest guidance by WHO assumes hospitalization rates of 6% among high-risk individuals and 3% among moderate risk individuals\(^b\)(2), applying the pooled estimates for hospitalization for these risks, the NNT would be 29 among high-risk patients and 58 among moderate risk patients. Based on this risk assessment, WHO strongly recommends nirmatrelvir/ritonavir for people at high risk and moderate risk of hospitalization.

This meta-analysis was based mostly on observational studies of varying quality, in which immortal time bias and residual confounding were common.

In the Paxlovid® trial, rebound COVID-19 episodes have been documented both in treated and untreated patients (around 2% in both), including fully vaccinated patients. A brief drop of symptoms and PCR positivity might be the natural course of SARS-Cov2 infection. Cases of rebound after treatment with Paxlovid® reported until now are mild and no additional treatment is needed. No resistance to Paxlovid® has been shown. Possible transmission has been reported, so restarting isolation measures as by Sciensano protocol is still required (COVID-19 Rebound After Paxlovid Treatment (cdc.gov)).

### 1.14 Camostat mesylate

**Main message**

There is no published evidence for clinical efficacy of this drug for COVID-19. This drug is currently unavailable for treatment outside of clinical trials in Belgium.

**Available evidence**

Camostat mesylate is a serine protease inhibitor used in Japan, which is being evaluated as a repurposed drug after it has shown to reduce SARS-CoV-2 infection of primary human lung cells (Calu-3 cell line) *in-vitro* (208). Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (e.g. NCT04355052 (Israel), NCT04321096 (Denmark)).

---

\(^b\) Patients at *high* risk of hospitalization includes those with diagnosed immunodeficiency syndromes, those who have undergone solid organ transplant and are receiving immunosuppressants, and those with autoimmune illness receiving immunosuppressants.

\(^b\) Patients at *moderate* risk of hospitalization are those over 65 years, those with obesity, diabetes and/or chronic cardiopulmonary disease, chronic kidney or liver disease, active cancer, those with disabilities, and those with comorbidities of chronic disease (2)
Available evidence in the hospital setting

The first results of the Danish RCT among 205 hospitalized patients (137 treated with camostat mesylate, 200 mg t.i.d. for 5 days, vs 68 treated with placebo) shows that this drug is safe, but it had no viral nor clinical added benefit compared to standard of care (209).

Available evidence in the ambulatory setting

The results of early treatment in ambulatory patients are still awaited. A phase 2 trial in ambulatory patients looking for antiviral activity is ongoing in UZ Gent. Large multi-country trials with clinical endpoints are ongoing and a trial is approved in the ambulatory setting in the KUL.

1.15 Fluvoxamine

Main message

Two independent RCTs (one large and one small) and two observational studies have shown that fluvoxamine early treatment is associated with prevention of clinical deterioration in outpatient, at-risk subjects (210,211). The effect on robust clinical endpoints such as hospitalizations or deaths is not fully established, and it is unclear whether it could be beneficial in a fully vaccinated population (with lower baseline risk of complications). For the moment, no strong recommendation can be made for early administration of fluvoxamine or similar drugs in high-risk outpatients. Data on in-hospital patients are scarce, with so far only one observational trial in an ICU population that showed lower overall mortality in the group that received fluvoxamine in addition to standard of care (212). In a meta-analysis that combined the available studies on hospitalized and ambulatory patients, the authors concluded that fluvoxamine had a beneficial effect on mortality or hospitalization rate with an OR of 0.45 (95% CI, 0.28-0.72) (213).

Nevertheless, the quality of studies is poor. Data from RCT are needed before we can recommend this treatment.

Fluvoxamine is a SSRI antidepressant drug but also a strong S1R agonist associated with reduction of inflammation during sepsis. It also has possible anti-platelet activation properties (214).

Available evidence in the hospital setting

An open-label prospective cohort trial with matched controls included 51 COVID-19 patients who met criteria for severe disease and were admitted to the ICU in two university hospitals in Croatia. They were treated with fluvoxamine 100 mg three times daily for 15 days in addition to standard therapy and were prospectively matched for age, gender, vaccination against COVID-19, disease severity and comorbidities with 51 ICU controls. No statistically significant differences between groups were observed regarding the number of days on ventilator support, duration of ICU, or total hospital stay, but overall mortality was lower in the fluvoxamine group, 58.8% (n= 30/51), than in the control group, 76.5% (n= 39/51), HR 0.58, 95% CI (0.36-0.94, p= 0.027) (212).

Available data in the ambulatory setting

A small pilot placebo-controlled trial (n= 80 and n=72 subjects in the fluvoxamine and placebo groups respectively) found a significant difference in the rate of clinical deterioration (0% vs 8%; p=0.009). Dosage used in this pilot trial was 50 mg day 1, then 100 mg BID for 2 days then 100 mg TID until day 15 (215). A larger placebo-controlled trial (TOGETHER) in Brazil (n= 741 and n= 756 in the fluvoxamine and placebo groups, respectively, the vast majority of participants were not vaccinated) found a significant decrease of a composite primary outcome event (hospitalization OR stay > 6h in the emergency room) (10.7% vs 15.7%). In secondary analysis, mortality was also decreased in the per-protocol fluvoxamine group vs placebo (1 vs 12 deaths), but the difference was not significant in the intent-to-treat population. Dose used was 100 mg BID for 10 days (216). A large (n=1431) multicentric, randomized, double blind, placebo-controlled trial (COVID-OUT) investigating three different repurposed drugs (metformin, ivermectin, fluvoxamine) in early COVID-19 infection (< 7 days since symptom onset) in non-hospitalized at-risk patients showed no significant reduction in the occurrence of the compositive endpoint (hypoxemia, emergency department visit, hospitalization or death) with any of these three drugs (217).

As the current evidence for the use of fluvoxamine in the outpatient setting remains contradictory and poorly conclusive, this drug should be discouraged in this population for the moment, pending ongoing trials.
1.16 Azithromycin

As there is significant evidence to support that this treatment is not recommended, the follow-up of this evidence is no longer a priority and might no longer be up to date.

Main message
Despite some initial interest based on in- vitro data, large clinical trials (e.g. RECOVERY) have not demonstrated improved clinical outcomes among COVID-19 patients (both in in and outpatients).

Available data in the hospital setting
Azithromycin, shown to have some antiviral and immunomodulatory effect, has been promoted by some groups based on observational viral and clinical data (218). The potential benefit of using AZM alone or with other drugs has not been demonstrated so far. Two large RCTs in Brazil have explored the usefulness of this drug in association with HCQ, both in mild/moderate (171) and severe hospitalized patients (28), and did not find any added value compared to HCQ alone. The azithromycin arm of RECOVERY was closed on November 27, 2020 for futility, after 2582 patients were randomized to azithromycin and compared to 5182 patients receiving standard of care. No effect was observed on 28-day mortality, nor on the risk of progression to mechanical ventilation or on length of hospital stay (219). The results of DAWN-AZITHRO are also expected soon.

Available evidence in the ambulatory setting
No published data.

1.17 Ivermectin

Main message
Currently there is insufficient high-quality evidence to justify the use of ivermectin. In line with WHO and EMA, we recommend against the use of ivermectin in clinical care.

Available evidence
In vitro inhibition of SARS-CoV-2 replication in Vero/hSLAM cells has been reported with ivermectin (IVM), but at concentrations 50 to 100 times higher than those clinically attainable in human patients (150-400 µg/kg). Preliminary evidence based on compilation of observational studies suggested survival benefit in ivermectin recipients (OR, 0.27; 95% CI, 0.09–0.80; P< 0.03) (220).

Available evidence in the hospital setting
No effect was shown on viral clearance, clinical recovery or survival. Please see below.

Available evidence in the ambulatory setting
Until now, 21 (12 double-blinded) RCTs studying the effect of ivermectin at different dosages on viral clearance, prevention, clinical recovery and survival have been published in peer-reviewed journals (192–211). All but two excluded severe and critical COVID-19 patients and dosages of ivermectin varied between 100 µg and 400 µg/kg (single doses up to 5 consecutive days). One trial studied the efficacy of an ivermectin nanosuspension nasal spray (228). Seven of these studies showed a more rapid decline in viral load. None of these studies demonstrated any differences in resolution of symptoms or mortality, except five (two of which non-blinded) RCTs demonstrating significantly less development of symptoms in asymptomatic patients when treated with a single dose of ivermectin (240), more rapid resolution of anosmia (111), less progression to severe illness (241), and more rapid clinical improvement (228,231,241). A systematic review and meta-analysis of RCT’s concluded that ivermectin did not reduce all-cause mortality, length of stay or viral clearance in COVID-19 patients with mostly mild disease (242). Many of the available RCTs show several methodological issues such as small sample size, lack of blinding, various drugs in the control arms, different clinical scenarios (as prophylaxis, early outpatient administration and later treatment in admitted patients) and/or incomplete data on outcomes, as summarized in a Commentary in British Medical Journal (BMJ) Evidence-Based Medicine (243). Based on the current low to very low evidence, a Cochrane systematic review on ivermectin as treatment or prevention of COVID-19 in in- and outpatients failed to demonstrate its efficacy or safety and does not support its use outside of well-designed RCTs (244). In March 2022, the results of the large TOGETHER platform trial in Brazil demonstrated in a conclusive manner that Ivermectin (400 µg/Kg) daily for 3 days, administered within 7 days of symptom onset in 679 COVID-19 outpatients with at least one risk factor
of disease progression, did not reduce the need for hospital admission/ prolonged stay in the emergency department compared to placebo. This trial substantially adds to the body of evidence that ivermectin is not effective against COVID-19, even when administered early-on in the disease (245). Furthermore, a large (n=1431) multicentric, randomized, double blind, placebo-controlled trial (COVID-OUT) investigating three different repurposed drugs (metformin, ivermectin, fluvoxamine) in early COVID-19 infection (< 7 days since symptom onset) in non-hospitalized at-risk patients showed no significant reduction in the occurrence of the composite endpoint (hypoxemia, emergency department visit, hospitalization or death) with any of these three drugs (217).

Of note, a correspondence in the N Engl J Med warns about the risks of severe ivermectin toxicity (including ataxia, visual disturbances, convulsions,…leading to hospital admission) when misused at high dosages for treatment or prevention of COVID-19 (246).

The results of the COVID-OUT trial add conclusively on the already convincing evidence that ivermectin has no place in the outpatient treatment of COVID-19. In line with WHO and EMA, we recommend strongly against the use of ivermectin in clinical care.

### 1.18 Colchicine

#### Main message

WHO made a strong recommendation against using colchicine for treatment of patients with non-severe COVID-19 and stated that it was unlikely future studies would identify subgroups of patients who may benefit from colchicine.

#### Available evidence in the hospital setting

Preliminary evidence from large trials (RECOVERY) did not find any clinical benefit of this drug for hospitalized COVID-19 patients. Earlier administration in PCR-diagnosed ambulatory patients seemed to provide a marginal benefit in preventing hospital admission in a large RCT (COLCORONA). A few observational studies using variable drug dosages have been published, suggesting a possible clinical benefit (247). One small open-label RCT has evaluated the efficacy of colchicine for hospitalized patients (one third of the patients however did not require oxygen at inclusion) (248). No patient received corticosteroids as part of SOC treatment. The trial showed a significant reduction in clinical deterioration and an improvement in terms of time to clinical deterioration in the colchicine group. It should be noted that recruitment was terminated prematurely due to slow patient accrual, with 105 of 180 planned inclusions. A second RCT including 75 moderately to severely ill patients (a majority of them also treated with corticosteroids) showed a reduction of the duration of both oxygen supplementation and hospitalization among colchicine-treated patients. ICU admission and death were rare in both groups (249). Two systematic reviews of eight studies (some of them pre-print) with heterogeneous design and varied “control” arms both in out- and inpatients suggested some survival benefit and concluded that large RCTs were still needed. The current evidence does not permit to recommend for or against use of colchicine in the treatment of COVID-19 until data from larger RCTs are published. However, according to the results of an arm of the RECOVERY trial, there was no demonstrated benefit of colchicine in addition to steroids (in terms of mortality at Day 28, duration of hospital stay or progression to mechanical ventilation) in patients hospitalized with COVID-19 (250). A smaller RCT (n=103) evaluating colchicine in hospital patients reached the same conclusions. These observations strongly suggest that colchicine has no place in patients admitted for severe/critical COVID-19 (251).

#### Available evidence in the ambulatory setting

A large multicenter placebo-controlled RCT evaluated colchicine (2 x 0.5 mg for 3 days followed by 0.5 mg/day for one month) in > 4000 PCR-confirmed COVID-19 ambulatory patients with risk factors for severe covid (being age, main comorbidities, fever or a set of full blood count abnormalities) (252). The trial showed no significant effect of colchicine on the combined primary outcome (death or hospitalization) when considering all included cases (4.7% vs 5.8%, OR 0.79, p=0.081) but showed a reduction of this outcome when considering the prespecified group of PCR-proven cases (4.6% vs 6%, OR 0.75, p=0.042). There were two times more diarrhea in the colchicine group than in the placebo group (13.7 vs 7.3%; p<0.001). The trial was stopped at 75% of planned recruitment, due to organizational constraints. As discussed in the accompanying editorial, these findings do not imply that colchicine will likely become the first-line community treatment for early COVID-19, because the effect size was small, and the number needed to treat large (70). It adds however some evidence that anti-inflammatory drugs administered early in the course of the disease may be beneficial (253).
1.19 Aspirin

As there is significant evidence to support that this treatment is not recommended, the follow-up of this evidence is no longer a priority and might no longer be up to date.

**Main message**

Aspirin has demonstrated no clinical benefit in two large trials among hospitalized patients across different forms of disease severity and should not be used in the management of COVID-19.

Aspirin (ASA) is a non-selective inhibitor of COX-1 and COX-2 enzymes leading to a decreased production of prostaglandins, thromboxane A2 by platelets. Low dose ASA is associated with antithrombotic effect. Patients with septic shock have decreased risk of DIC when using ASA.

**Available evidence in the hospital setting**

One retrospective study found a decreased risk of mechanical ventilation, ICU admission and in-hospital mortality among patients admitted with COVID-19 (254). Different cohort studies have shown a decreased risk of acute lung injury/ARDS in patients on chronic ASA-treatment.

Dozens of RCTs are evaluating ASA in COVID-19 in addition to standard of care. By press release, RECOVERY trial announced that Aspirin (150 mg daily) has no impact on mortality as compared to standard of care in hospitalized patients ([link](#)). Similar findings were announced for critically ill patients in the REMAP-CAP trials.

**Available evidence in the ambulatory setting**

No data.
2 GENERAL NOTES

2.1 ACE inhibitors or ARBs

There is currently no evidence from clinical or epidemiological studies that establishes a link between their use and severe COVID 19 (255,256). An RCT found no impact of ACEi/ARB switch in COVID-19 (257). The same types of concerns were raised for non-steroidal anti-inflammatory drugs (NSAIDs), with also no evidence so far to advise for or against these drugs in COVID-19 patients. A nationwide cohort study in Denmark found no difference in COVID-19 outcome in patients with recent use of NSAID (258). However, to be safe, and while waiting pending results, paracetamol may be preferred as first-line symptomatic treatment of pain and fever (at usual dosage), while NSAIDs should be used with caution (as in common practice) and according to common practice (contra-indicated in case of renal failure for example).

2.2 Pregnant women

Specialized care and close monitoring for complications is absolutely necessary in COVID-19 pregnant women. A COVID positive patient, if maternal condition allows it, can deliver vaginally. Large organizations like WHO, RCOG and ACOG support the practice of breastfeeding even in the context of active SARS-CoV-2 disease, but with application of necessary preventive measures (mask, nipple cleaning, frequent handwashing). See additional guidance on newborns of COVID-19 positive mothers via the following link. Monoclonal antibody treatment of COVID19 confirmed pregnant women should be considered depending on the safety profile, maternal risk factors (diabetes, hypertension, asthma) and pregnancy outcome (possible risk of premature delivery in the setting of viral infection) (259). International guidelines are available, including from NIH, RCOG and WHO guidance.

The Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom regularly updates its clinical guidance for health professionals and pregnant women regarding COVID-19 in pregnancy.


2.3 Children

Specific guidelines are available: Traitement et prise en charge de l’enfant atteint de la COVID-19: Particularités pédiatrique/Opvang en behandeling van kinderen met COVID-19 gerelateerde ziekte (online on 1 December 2020):

FR:  

NL:  

2.4 Anticoagulation in COVID-19 patients

Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease, with pulmonary embolism (as well as cerebrovascular accident or myocardial infarction) regarded as important risk factors for increased mortality. Indeed, an open-label, international, adaptive, multiplatform, randomized, controlled trial where three platform trials were integrated into a single trial (ATTACC, ACTIV-4a, and REMAP-CAP), to evaluate whether therapeutic-dose anticoagulation may improve outcomes in noncritically ill patients hospitalized with COVID-19, compared to usual care thrombo-prophylaxis. 2219 patients were included in the final analysis, when prespecified criteria for superiority of therapeutic-dose anticoagulation were met. Initial therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge (98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58), with less use of cardiovascular or respiratory organ support as compared with usual-care thrombo-prophylaxis (260).

On the other hand, an open-label, international, adaptive, multiplatform, randomized, controlled trial where three platform trials were integrated into a single trial (ATTACC, ACTIV-4a, and REMAP-CAP), to evaluate whether therapeutic-dose anticoagulation may improve outcomes in critically ill patients hospitalized with COVID-19, compared to usual care thrombo-prophylaxis. This trial was stopped after 1098 patients were included based on pre-defined criterion for futility for therapeutic-dose anticoagulation. This trial did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis (261).
A consensus guideline on anticoagulation management in COVID-19 positive patients has been published by the Belgian Society on Thrombosis and Haemostasis and available here. Of note, a KCE report on thrombo-prophylaxis in COVID-19 diseases concluded that the BSTH management algorithms are of good quality and in agreement with international guidance.

2.5 Oxygen therapy in COVID-19 patients

A working group coordinated by AFMPS/FAGG has prepared guidelines for oxygen therapy in:
1. Hospitalized patients: FR, NL
2. Patients after hospital discharge and residents of nursery homes: FR, NL

2.6 Ambulatory care

Treatment of COVID-19 patients in nursing homes: Collège de Médecine Générale: Mise à jour du protocole thérapeutique des résidents d’institutions âgés de plus de 75 ans atteints de Covid-19:


Superior Health Council advice on Vitamin D, Zinc and COVID-19

Outpatient care for Covid-19 patients in the context of saturation in Belgian hospitals

APPENDIX 1. AVAILABILITY OF REMDESIVIR

This annex explains how to access remdesivir.

The medicine Veklury (remdesivir) is available in the strategic stock, stored and distributed by a State-designated distributor. It is available to hospitals for patients that fill the criteria for use as defined in this guidance. Hospital pharmacists have been informed on the procedure to obtain Veklury. The FAMHP closely monitors the evolution of stocks and, if necessary, places new order to ensure sufficient supply.

Veklury is registered for the treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg). For pregnant women and children <12y, compassionate use is possible (as stated in art 107/1).

When using Remdesivir for compassionate use, a notification to umn@fagg#afmps.be and to the ethics committee of the concerned site is to be made.

If you have problems obtaining the medicinal products in this guideline, please contact supply-problems@fagg#afmps.be

APPENDIX 2. SAFETY PROFILES

Safety profiles can be found at www.BCFI.be (SKPs), www.CBIP.be (RCPs) or via https://geneesmiddelendatabank.fagg#afmps.be/

More information via www.ema.europa.eu (European Medicines Agency)

Any suspected adverse events related to these drugs should be reported through the usual channels, as part of regular pharmacovigilance activities: www.notifieruneffetindesirable.be or https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar

APPENDIX 3. PRACTICAL ASPECTS CONCERNING ADMINISTRATION OF PAXLOVID® (NIRMATRELVIR+RITONAVIR)

Since 24 February 2023, Paxlovid® received a full marketing authorisation by EMA for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe. Although authorized for use by the EMA, clinicians should be aware of several limitations. First, ritonavir is a strong cytochrome P450 3A4 inhibitor, causing many drug-drug interactions. Second, there is almost no data on the efficacy of this drug in immunocompromised patients, or in patients taking drugs that could cause drug-drug interactions with ritonavir. Indeed, the EPIC-HR trial was stopped early due to the demonstrated efficacy of Paxlovid® in the interim analysis, and exclusion criteria in the study were the use of any drug that was highly dependent on CYP3A4 during treatment and for 4 days after the last dose of nirmatrelvir/ritonavir, or the use of a potent CYP3A4-inducing drug (193). Third, the drug cannot be administered to patients with renal insufficiency with a creatinine clearance < 30 mL/minute, or those with severe hepatic insufficiency.

The treatment should be administered as soon as possible, and definitely within 5 days of symptoms onset.

Dosage regimen of Paxlovid® in function of creatinine clearance (mL/minute)

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/minute)</th>
<th>Dosage nirmatrelvir (mg)</th>
<th>Dosage ritonavir (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>300 BID</td>
<td>100 BID</td>
</tr>
<tr>
<td>≥ 30 to &lt; 60</td>
<td>150 BID</td>
<td>100 BID</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Contra-indicated</td>
<td>Contra-indicated</td>
</tr>
</tbody>
</table>
**Proposition of how to handle drug-drug interactions (link for NIH guidelines)**

<table>
<thead>
<tr>
<th>Concomitant medications requiring patients to receive an alternative COVID-19 therapy. This list is not exhaustive.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ergot derivatives</td>
</tr>
<tr>
<td>Flecaïnid</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
</tbody>
</table>

*Here is a list of the contra-indicated drugs provided by the [EMA.](#)*

<table>
<thead>
<tr>
<th>Concomitant medications that should be temporarily withheld, if clinically appropriate. Drug monitoring may be required. This list is not exhaustive.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Clonazepam</td>
</tr>
<tr>
<td>Chemotherapy (kinase inhibitors, vinca alkaloids, BCL-2 inhibitor venetoclax)</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Erythromycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant medications that require dose adjustments/ drug monitoring. This list is not exhaustive. To make dose adjustments, check the Liverpool COVID-19 Drug Interactions website (<a href="#">link</a>).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
</tr>
<tr>
<td>Amlodipine</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Itraconazole</td>
</tr>
<tr>
<td>Ketoconazole</td>
</tr>
</tbody>
</table>

**Used definition of severely immunocompromised patients:**

- Hematological malignancy
- Solid cancer undergoing cytotoxic treatment
- Solid organ or hematopoietic stem cell transplantation
- Patients who are within 1 year of receiving B-cell depleting therapies (e.g. rituximab, ocrelizumab, alemtuzumab, etc.)
- Primary immune deficiency
- HIV with CD4 <200/mm³ and/or detectable viral load
- Patients chronically treated with corticosteroids > 20 mg of prednisolone or equivalent per day
- Patients chronically treated with methotrexate > 20 mg/week
- Chimeric antigen receptor T cell recipients (CAR-T cell therapy)
- Patients treated with immunosuppressive drugs such as anti-proliferatives (azathioprine, mycophenylate mofetil), calcineurin inhibitors (tacrolimus, cyclosporine, etc.), CTLA-4 agonists (abatacept), JAK inhibitors (baricitinib, ruloxitinib, tofacitiniib, etc.).
- Patients undergoing dialysis
REFERENCES


211. Hoertel N, Sánchez-Rico M, Herrera-Morueco JJ, de la Muela P, Guibins E, Kornhuber J, et al. Comorbid medical conditions are a key factor to understand the relationship between psychiatric disorders and


