INTERIM CLINICAL GUIDANCE FOR ADULTS WITH SUSPECTED OR CONFIRMED COVID-19 IN BELGIUM

18 July 2020; Version 12

1. Preliminary note

This document has been revised on the 18 July 2020 to provide support to the diverse groups of Belgian clinicians (general practitioners, emergency physicians, infectious disease specialists, pneumologists, intensive care physicians) who have to face suspected/confirmed COVID19 cases, during the epidemic in Belgium.

The guidance has been first developed by a task force: Dr Sabrina Van Ierssel, Universitair Ziekenhuis Antwerpen, UZA (Sabrina.VanIerssel@uza.be); Dr Nicolas Dauby, Hôpital Universitaire Saint-Pierre Bruxelles, HSP (Nicolas_Dauby@stpierre-bru.be); Dr Emmanuel Bottieau, Instituut voor Tropische Geneeskunde, ITG (ebottieau@itg.be), and Dr Ralph Huits, ITG (rhuits@itg.be). It was initially based on the therapeutic protocols elaborated in the two reference institutions (UZA and HSP). It has been revised in fast track by a larger group of physicians and scientists from different specialties/disciplines including experts from ScienSano (Dr Chloe Wyndham-Thomas at Chloe.WyndhamThomas@sciensano.be) and from AMPS/FAGG (Dr Roel Van Loock at Roel.VanLoock@fagg-afmps.be). It is based on the best (but very incomplete) clinical evidence that is currently available, and is purposed to become a “living guideline” which will be regularly updated each time new relevant scientific data will emerge (latest version will always be found via the same link). Keeping the guidance 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 comment, relevant publication, including from the grey literature, and contribution in priority to the small core group (ideally to all six provided mails). We thank the countless readers who, since this guideline was initially released, flagged the inconsistencies, typo’s or unclarities, as well as those who sent all types of contribution with regards to this rapidly evolving field.

COVID-19 is a mild viral illness in the vast majority of the patients (80%) but may cause severe pneumonitis and disseminated endotheliitis [1] (and subsequent complications) with substantial fatality rates in elderly and individuals with underlying diseases. About 20% of infected patients need to be admitted, including 5% who require intensive care. A study has shown that case severity is correlated with viral load, irrespective of symptoms duration [2]. Mortality in admitted patients reached 25% in the middle of the epidemic in Wuhan [3]. In Lombardy, mortality reached 26% in patients admitted to intensive care units [4]. This document will not elaborate in detail the generic and supportive management of such infections (except if there are some pathogen-specific interventions). It is also not aimed at providing a new extensive review on all potential investigational treatments in the pipeline. We have opted for a short document with synoptic Tables summarizing:

1. the selected investigational drugs to consider for CLINICAL USE at this moment in Belgium, with information on in vitro/in vivo efficacy (Table 1);
2. the current therapeutic recommendations for each category of COVID-19 patients, with indications and precautions (Table 2);
3. the clinical trials ongoing in Belgium (Table 3);
Rows will be added or subtracted to these Tables according to new evidence and recommendations, through regular updates. A considerable number of clinical trials (lists not exhaustive in Table 1) are ongoing or being initiated globally, that should provide several key answers on the best therapeutic options in the next future.

**IMPORTANT:**

As a rule, only manuscripts ACCEPTED after a rigorous PEER-REVIEW process will be referred to for the strong recommendations in this guideline. 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 in clinical studies/trials and efforts are undertaken by the KCE to support non-commercial multicentric studies in Belgium. In addition, use of standardized case report form is strongly encouraged during patient management, in order to obtain a fast feedback on safety issue and patient outcome.

Of note, lopinavir/ritonavir, (hydroxy)chloroquine or IL1/IL6 blockers are drugs registered in Belgium for other indications (off label use), so that the normal pathway for notification of adverse events has to be used, unless prescribed in the context of a clinical trial. For compassionate use of investigational drugs such as remdesivir and import of chloroquine base, please refer to Annex 1.

### 2. Summary of efficacy data of selected drugs

**Table 1 : In vitro / in vivo efficacy of antiviral drugs selected for treatment of suspected/confirmed COVID-19**

*Note: all ongoing clinical treatment trials/studies over COVID-19 (> 300) are compiled in a real-time dashboard at LitCovid website, see The Lancet [5]; we try to summarize the relevant information for the selected drugs*

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro activity</th>
<th>In vivo activity (animal models)</th>
<th>Clinical studies (non-exhaustive)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SARS-CoV-1</td>
<td>MERS-CoV</td>
<td>SARS-CoV-2</td>
<td>SARS-CoV-1</td>
</tr>
<tr>
<td>Remdesivir / GS5734</td>
<td>+++ [6,7]</td>
<td>+++ [6–9]</td>
<td>+++ [10]</td>
<td>+++ [11]</td>
</tr>
<tr>
<td>(available in Belgium only in compassionate use or within trials)</td>
<td>Ongoing for SARS-CoV-2 NCT04252664 (suspended) NCT04257656 Terminated: no survival benefit could be demonstrated (see details below) [12]</td>
<td>Interactions with viral polymerase [6,9]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 via [www.notifieruneffetindesirable.be](http://www.notifieruneffetindesirable.be) or [https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar](https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar)
Under investigation in Solidarity (WHO) and DisCoVeRy (INSERM) trials, but not in Recovery (UK).

Faster recovery demonstrated in a preliminary report of the RCT NCT04280705 (results on mortality by day 28 still pending) [13]

**Chloroquine phosphate (CQ)**

(not marketed in Belgium, but available via import; also available as magistral preparation as chloroquine phosphate; 500mg chloroquine phosphate = 300mg chloroquine base;)

Used for malaria

<table>
<thead>
<tr>
<th></th>
<th>+++</th>
<th>++</th>
<th>++</th>
<th>+/-</th>
<th>Not studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine phosphate (CQ)</td>
<td>[14,15]</td>
<td>[16]</td>
<td>[10]</td>
<td>[17]</td>
<td></td>
</tr>
</tbody>
</table>

Although in initial Solidarity (WHO) protocol, the trial was only ever pursued with hydroxychloroquine (cfr below)

Fusion and uncoating blockade, by lysosomal alkalization [14,15]; Interaction with the ACE2 receptor [14]; “immunomodulation”?+++

**Hydroxy-chloroquine (HCQ) (Plaquenil®);**

Used for lupus, rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>+/-?</th>
<th>Not studied</th>
<th>+++</th>
<th>Not studied</th>
<th>Not studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxy-chloroquine (HCQ)</td>
<td>[18]</td>
<td></td>
<td>[19]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ongoing for SARS-CoV-2 NCT04261517

Reduction of the proportion of SARS-CoV-2 RNA positivity (RT-PCR) in nasopharyngeal swabs of treated patients compared to external control group with symptomatic care only (weak evidence) [20]

Was under investigation in the SOLIDARITY (WHO), RECOVERY (UK) and DisCoVeRy (INSERM) trials, at high dosages (9600 mg in total over 10 days for the former two trials and 5600 mg in total over 10 days for the latter). All three trials stopped enrolling

Not fully elucidated but assumed to be similar to that of chloroquine
patients in hydroxychloroquine arm: no clinical benefit in patients hospitalized with COVID-19 (press releases)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Efficacy</th>
<th>Viral Clearance</th>
<th>Radiological Evolution</th>
<th>Safety Profile</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>+/-</td>
<td>-</td>
<td>Not studied</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>(Kaletra®)</td>
<td>[21–23]</td>
<td>[24]</td>
<td></td>
<td>[8,25]</td>
<td></td>
</tr>
<tr>
<td>Used in HIV infection</td>
<td>Not studied</td>
<td>Not studied</td>
<td></td>
<td>Weak efficacy for SARS-CoV-1; associated with ribavirin &amp; corticosteroids [23]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discontinued in the SOLIDARITY because of lack of benefit (press release). Also discontinued in DisCoVeRy.</td>
<td></td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Not studied</td>
<td>Not studied</td>
<td>++</td>
<td>Not studied</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(at higher dosage than for influenza)</td>
<td>Shorer viral clearance time and improved radiological evolution compared to lopinavir/ritonavir (non-randomized) [28]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04373733</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04374019</td>
<td></td>
</tr>
<tr>
<td>Camostat</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>NCT04355052</td>
</tr>
<tr>
<td></td>
<td>[31]</td>
<td>[31]</td>
<td>[31]</td>
<td>[32]</td>
<td>NCT04321096</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04353284</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04374019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inhibition of the activity of RNA dependent RNA polymerase (RdRp)[29,30]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04355052</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04321096</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04353284</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT04374019</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inhibition of TMPRSS2, a cellular serine protease, that primes SARS-CoV-2 Spike (S) protein for cell-entry [31]</td>
<td></td>
</tr>
</tbody>
</table>

**Note**: Many other antiviral/immunological treatments have been/are being investigated, including (list not exhaustive) ribavirin, favipiravir, convalescent plasma, monoclonal antibodies, complement inhibitors etc. see Landscape analysis of therapeutics WHO 17/02/2020, link. At this moment, any of these drug candidates should ONLY be evaluated in clinical trials (see below) and in Belgium, these trials should ideally be coordinated centrally.

Key points on safety profile are found in Table 2 and an extensive safety profile and/or SmPC of the proposed drugs can be found in Annex 2.
3. Belgian recommendations for supportive care and adjunctive antiviral/immunomodulatory treatment for suspected/confirmed COVID-19 cases, according to disease severity.

General guiding principles

Clinical efficacy of antiviral therapy in SARS-CoV-2 is likely to be time-dependent. For example, administration of chloroquine before inoculation of SARS-CoV-2 onto Vero6-cells, showed greater inhibition of virus replication than simultaneous or later administration [10]. Similar to the use of antiviral therapy in other (unrelated) infections, e.g. oseltamivir in affecting outcomes in influenza infections, pharmaceutic inhibition of virus replication should be administered as early as possible after symptom onset [33,34].

However, absence of clinical evidence so far and limited immediate availability of several potential therapies do not allow to recommend systematic early treatment with antivirals at this moment (see recommendations below).

- Chloroquine and hydroxychloroquine inhibits replication of SARS-CoV-2 in vitro. Chloroquine (CQ) inhibits the virus at concentrations (EC50 = 1.13 to 5.47 µM) that cannot be achieved in human plasma [10], but possibly in the intracellular compartment. This drug (not available in Belgium since 2015) has been used for decades (at a total of 25 mg/kg within 3 days) for malaria treatment without any monitoring and side effects, including in pregnant women. However, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages [19].

Hydroxychloroquine (HCQ, drug marketed in Belgium as Plaquenil®) has appeared to be more potent than chloroquine in vitro (EC50=0.72 µM), so that lower dosages (than initially recommended) could be used [19]. It has also a better safety profile than chloroquine (larger therapeutic window). Based on these limited pharmacokinetic data, a risk/benefit balance, and some preliminary results of small clinical studies, off-label administration of “low-dose” hydroxychloroquine sulphate had been recommended in Belgium for ADMITTED patients during the epidemic: 400mg BID on day 1, followed by 200mg BID on day 2-5, for a total of 2,400 mg (with clear precautions of use, annex 3). Since the risk/benefit balance was considered less favorable, the hydroxychloroquine treatment was not recommended for outpatient use in mild COVID-19, even in patients at highest risk of complications (risk of toxicity versus uncertain benefit).

Similarly, there was no recommendation to combine azithromycin with hydroxychloroquine outside clinical trials (no clear data on antiviral activity of azithromycin, and risk of increased cardiac toxicity, as reported in France [35]).

Several small retrospective studies could not demonstrate any independent benefit of hydroxychloroquine use compared to non-exposed patients [36–39]. Some larger retrospective studies did find an independent association between HCQ use (low dosage, similar to the “Belgian” recommendations) and a reduction in COVID-19 associated mortality [40,41]. However, the major limitation of all these studies was the retrospective observational design that precluded any definitive conclusion about treatment efficacy. The prospective randomized controlled trial RECOVERY in UK has 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. Peer-reviewed publication of the preliminary results are awaited (link). For the same reason (absence of efficacy in hospitalized patients), the SOLIDARITY trial has communicated the suspension of recruitment in the HCQ arm (9600 mg over 10 days) on 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. A first randomized controlled trial using HCQ 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 infection in 85% of the participants. No serious adverse events were notified. The results of several other ongoing trials using HCQ in PrEP, PEP and early in mild ambulatory COVID-19 patients are still awaited.

Overall, based on these preclinical observations and the expected trial results it has been decided not to recommend its off-label use for COVID-19 in Belgium anymore (see V10, 5th of June), except within ongoing clinical registered trials, and after timely interim analysis of the study-related risk/benefit.

On a final note, the risk of serious adverse events associated with chloroquine and hydroxychloroquine has been also recently reanalyzed within the pharmacovigilance data from EudraVigilance by FAGG/AFMPS. Both drugs can cause heart rhythm problems via QTc prolongation, that could be exacerbated if combined with other medicines with similar cardiac effects. A total of 182 cases of QTc prolongation have been reported with hydroxychloroquine across Europe since the beginning of the epidemic (European Pharmacovigilance Database of the EMA, EudraVigilance, 20 May 2020) particularly when taken at high doses and/or in combination with the antibiotic azithromycin (or other drugs known to prolong the QTc interval) and/or with concomitant hypokalemia/hypomagnesemia. As of 26 May 2020, FAGG-AFMPS counted 8 cases of adverse reactions suspected to be associated with HCQ’s use for the treatment of COVID-19 in Belgium, among which 3 cardiac adverse reactions (no deaths reported among these 3 cases). It is also important to mention that Sciensano is currently analyzing the treatment and outcome data collected in the Belgian hospitals since the beginning of the epidemic, with a focus on HCQ impact.

- **Lopinavir/ritonavir** (LPV/r 400 mg/100 mg BID), initiated more than 12 days post symptom onset (median, IQR [11–17 days]) did not show clinical benefits in hospitalized patients with COVID-19. Moreover, there was no impact on viral excretion. This is in line with in vitro experiments with SARS-CoV2 but also SARS-CoV1. In this trial however, a possible benefit (clinical improvement) was suggested in patients who were treated before 12 days of symptom onset, HR 1.25 (0.77-2.05). Another small RCT conducted in China did not show any viral or clinical benefit however (or at best very marginal) [27]. Despite this lack of evidence, lopinavir/ritonavir could be considered a second choice for the moment, if remdesivir (see below) is not available but only if this treatment could be administered early in the course of the disease (within 12 days after symptom onset). We consider this treatment as futile if administered later on. WHO has announced that the Lopinavir/ritonavir arm was discontinued in the SOLIDARITY trial because of lack of benefit (4th July) ([link](#)). This arm was also stopped in RECOVERY (press release) and DisCoVeRy for the same reason. Finally, a benefit risk-assessment performed by the BRAT (Benefit-Risk Action Team) network and published on the 23 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 [42]. In light of these recent data, we no longer suggest off-label LPV/r as an alternative in severe COVID-19 disease. Its use should be limited within ongoing clinical registered trials.

- **Remdesivir** seemed promising in vitro and in non-human primates models [43]. An initial Chinese trial did not show any survival benefit with remdesivir, but the study could not include enough cases and was discontinued at the end of the local epidemic [12].

Meanwhile, a preliminary report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US has been published [13], showing a faster recovery in remdesivir-treated COVID-19 patients compared to patients given placebo (11 days instead of 15 days; recovery rate ratio 1.32; [95% CI 1.12 to 1.55], p<0.001). Such an effect was only seen in those COVID-19 patients receiving oxygen, the largest group of patients included in the study. But no effect was seen in patients not requiring supplemental oxygen, nor in patients requiring mechanical ventilation on Day 1. No statistical difference was seen for mortality by Day 14 (well
a positive trend compared to placebo: 7.1% mortality versus 11.9%; hazard ratio: 0.70; 95% CI 0.47-1.04). Mortality by Day 28 is not yet reported.

In addition, a randomized, open-label, phase 3 trial, comparing 5-day and 10-day treatment with remdesivir, 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 end points: 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 remdesivir treatment. Further evaluation of this subgroup and of other high-risk groups, such as immunocompromised persons, is needed to determine the shortest effective duration of therapy in these patients [44].

On 3 July 2020, following EMA evaluation, the European Commission has granted a conditional marketing authorization for remdesivir, for the treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg) with pneumonia who require supplemental oxygen (dosage and precautions see Table 2).

- **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 [45]. The half-life is approximately 5 hours. Therefore, higher dosing ranges are considered for the treatment of COVID-19 than for influenza (loading dose of 2400mg to 3000mg BID followed by a maintenance dose 1200mg to1800mg BID) [46]. In another non-randomized study, favipiravir showed shorter viral clearance time (4 days (IQR 2.5 - 9) vs. 11 days (8–13), p < 0.001)), significant improvement in chest imaging (91.43% versus 62.22% (p = 0.004)) and fewer adverse reactions compared with lopinavir /ritonavir [28]. Favipiravir has not been selected for these recommendations, as this molecule is not available in Belgium outside clinical trials.

- **Camostat mesylate** is a serine protease inhibitor used in Japan, which is being evaluated as repurposed drug after it has been shown to reduce SARS-CoV-2 infection of primary human lung cells (Calu-3 cell line) in vitro [31]. Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (NCT04355052 (Israel), NCT04321096 (Denmark). The drug is not available in Belgium.

- **Immunomodulatory agents** are a varied group of drugs that may have a (protective) role in the second phase of the disease, including the cytokine release syndrome, which seems driven by immunological mechanisms rather than direct viral pathogenicity. Several interleukin blockers seem promising according to clinical experience and small observational studies, including tocilizumab [47,48]. The manufacturer has announced that a faster recovery was observed in treated patients versus placebo, with even five days of treatment instead of ten days (data not yet available). These drugs are intensively investigated including in Belgium (see Table 3). There is no RCT evidence yet for recommending their use outside studies. Potential adverse events and drug interactions have to be carefully taken into consideration.

- **Convalescent plasma:** Animals studies with SARS-CoV-1 and SARS-CoV-2 infections indicate a protective role of neutralizing antibodies. Very limited evidence (uncontrolled case-series) suggest a potential benefit in COVID-19 patients [49]. A prematurely terminated randomized controlled trial in severely ill COVID-19 patients in Wuhan didn’t show faster clinical improvement nor decreased mortality in patients receiving convalescent plasma. But this study was underpowered and plasma was administrated late in the disease [median time from symptom onset to randomization: 30 days] [50]. Administration of convalescent plasma must only be considered within clinical trials such as the multicentric study DAWN-plasma that is currently ongoing. Both Rood Kruis and Croix Rouge are collecting plasma from patients who have
experienced COVID-19. Whenever possible, patients should be informed at discharge on the possibility to donate plasma and to contact their local RK/CR center. AFMPS/FAGG has recommended that donation should only take place more than 28 days after symptoms have ended.

- **Corticosteroids:** In accordance with WHO interim guidance [51] and a Correspondence in the Lancet [52], corticosteroids have been up to now not recommended as a systemic adjunctive treatment. Low dose dexamethasone (6 mg/day once daily for 10 days) is a treatment option which has been however investigated in one of the RECOVERY study arms. On the 16th of June, the RECOVERY investigators announced in a press release that recruitment to the dexamethasone arm was halted following the advice of the trial’s Steering Committee, as a sufficient number of patients (n=2104) had been enrolled in this study arm, and information for primary outcome was available for over 99.9% of them. Compared to 4321 patients randomized to usual care alone, 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) [53]. 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 (the majority of admitted patients), the task force recommends low dose dexamethasone for admitted patients requiring oxygen, in particular requiring mechanical ventilation and with a symptom onset > 7 days.

Table 2 is aimed to provide some guidance for adjunctive antiviral/immunological treatment (together with optimal supportive care). Comments and suggestions for clarity and feasibility are more than welcome by the writing team. As written above, the latest version of this clinical guidance will always be found via the same link. For all procedures with regards to patient general management (clinical assessment, testing, isolation, reporting etc.), please refer to procedures available at [https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV_procedures.aspx](https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV_procedures.aspx). Please note that these Sciensano procedures are also continuously being updated according to the evolution of the epidemic and new clinical evidence. To receive the alerts on procedure or clinical guidance updates, please subscribe at [https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV.aspx](https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV.aspx). For more specialized care (pneumology, cardiology, nephrology, transplantation medicine,…), please refer to the Belgian or international recommendations of professional societies. In the next version of this guidance, some COVID-19 specific guidance for subspecialties will be provided in a snapshot, with reference to relevant sources (with links).

**Note - 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 [54,55]. It is important that patients do not interrupt their treatment with ACE inhibitors or ARBs nor be switched to other medicines, in spite of concerns raised in the social media related to the theoretical interferences between ACE2 receptors (used for viral entry). The same type 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. By safety however 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 usually) and according to common practice (contra-indicated in case of renal failure for example).

**Note - pregnant women**

There is paucity of data on effects of COVID infection on pregnant women and neonates. There is currently no evidence that pregnant women are more at risk to get infected or to do more severe complications linked to COVID-19 (no maternal deaths in a series of 38 pregnant patients [56]. No transplacental transmission through the birth canal of the SARS-CoV-2 to the fetus has been demonstrated so far. No virus has been isolated from placenta, amniotic fluid or breastmilk. One neonate (born from a COVID-19 positive mother) tested COVID-19 positive 36 hours after birth, probably linked to close contact and droplets from the mother [57,58]. Mother-to-child perinatal COVID transmission has also been described in three neonates all born by caesarean section and transmission occurred despite implementation of strict IPC measures [59]. The three neonates had a favorable outcome and only mild COVID-19 disease, comparable with reassuring data on older children (initially in a series of 2000 Chinese children no deaths were described in those below 10 years old) [60,61]. Specialized care and close monitoring for complications is absolutely necessary. A COVID positive patient if maternal condition allows it can deliver vaginally. WHO recommends breastfeeding only if patient is using appropriate PPE (mask, nipple cleaning, frequent handwashing) [62]. See additional guidance newborns of COVID-19 positive mothers via the following link. Antiviral 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) (see also SmPCs in annex 2) [58]. Remdesivir is available for compassionate use in pregnant women with severe disease. A working group is preparing a more elaborated guideline for COVID-19 and pregnancy, to which we will refer as soon as finalized.

**Note - children:**

Specific guidelines are now available: *Belgian Pediatric COVID Guidelines for hospitalized children (non-PICU, based on the evidence available until 31/3/2020)*:


**Note – 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 an important risk factors of increased mortality. High incidence rates of severe pulmonary embolism, exceeding 10%, in COVID-19 ICU patients have been indeed observed (unpublished data, Strasbourg, Lille, Grenoble, and Cremona-Italy) [63]. In a multicentric study in the Netherlands, a 31% cumulative incidence of thrombotic complications was recently reported in ICU patients with COVID-19, despite receiving standard doses thromboprophylaxis [64]. A hypercoagulable state in severe COVID-19 patients associated with poorer outcome is suspected. High levels of pro-inflammatory markers, fibrinogen, and fibrinogen/fibrin degradation products (including D-Dimers), prolonged prothrombin times and disseminated intravascular coagulation are also described [65–67]. To date, there is no published evidence on an additional benefit of prophylactic or therapeutic anticoagulation for the treatment of COVID-19. Nevertheless, available data and clinical
observations appear sufficient to warrant heparin-based anticoagulation for the management of COVID-19 patients [63,68,69]. Prophylactic use of LMWH (low molecular weight heparin) in hospitalized cases with COVID-19 is now unanimously accepted, like it would be in any other inpatient with systemic inflammatory/infectious illness. Use of “intensified prophylactic doses” or even “therapeutic doses” of LMWH regimens in individuals at very high risk of thromboembolic events are even suggested by some experts, but the exact dosage, the precise target subgroups of COVID-19 patients and the set of laboratory parameters to support such decision remain undefined at this moment.

Important note: no drug-drug interactions are expected with LMWH and the antivirals mentioned in the guidance. No major drug interaction is expected with IL-1/IL-6 blockers either.

We therefore currently suggest that:

- In COVID-19 hospitalized patients with chronic oral anticoagulant, consider replacing this therapy by curative LMWH therapy, due to multiple potential drug interactions and difficulties to monitor oral anticoagulation.
- Prophylactic LMWH is indicated in most (if not all) COVID-19 patients who require hospitalization, according to the local institutional protocols, with standard weight adjusted and renal failure dose adjustments.
- Physicians should be alert to the reported associations of thromboembolic events and COVID-19, and maintain a low threshold to investigate and diagnose these conditions (pulmonary embolism, stroke). Therapeutic LMWH doses should be reserved for patients with demonstrated thromboembolic events or high suspicion thereof.
- Usual precautions with regards to LMWH safety are of course applicable.

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.

**Note – 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]

**Note – Treatment of COVID-19 patients in ambulatory care and in nursing homes:**

A working group has started the development of evidence-based COVID-19 guidelines for general practice and primary care. This working group is composed of staff from the various Academic Centres of General Medicine, and with various primary care organisations (Domus Medica, SSMG, Collège de Médecine Générale) - under the coordination of Werkgroep Ontwikkeling Richtlijnen Eerste Lijn (WOREL – www.ebp-guidelines.be ). The following topics will be covered: testing, diagnosis and reporting, treatment and follow-up, infection protection, organization of care and standard procedures. The working group plans to complete a first part of the guidelines by October 2020. Once validated, the guidelines will be included in the ebpracticenet database, so that they can also be quickly consulted by general practitioners from their medical records and by all other primary care workers.
Table 2: Supportive & antiviral/immunomodulatory treatment of hospitalized patients with suspected or confirmed COVID-19

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Supportive Care</th>
<th>Additional therapy</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suspicion of COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Mild-to-moderate symptoms (no dyspnea)</td>
<td>Symptomatic treatment</td>
<td>No</td>
<td>Use paracetamol in first-line (usual dosage), and NSAIDs with caution (if really required)</td>
</tr>
<tr>
<td>➢ No risk group*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Suspicion or confirmed COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Mild-to-moderate symptoms (no dyspnea)</td>
<td>Symptomatic treatment</td>
<td>In clinical trials only</td>
<td>Use paracetamol in first-line (usual dosage), and NSAIDs with caution (if really required)</td>
</tr>
<tr>
<td>➢ Risk group²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Confirmed COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe disease ≥ 1 of the following:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Respiratory rate ≥30/min (adults); ≥40/min (children &lt; 5)</td>
<td>Optimal supportive care in hospital (WARD or ICU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Blood oxygen saturation ≤89%</td>
<td>Provide 02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ PaO2/FiO2 ratio &lt;300</td>
<td>Administer prophylactic LMWH if not contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Lung infiltrates &gt;50% of the lung field within 24-48 hours</td>
<td>Consider dexamethasone 6 mg once a day for up to 10 days (or until hospital discharge if sooner), IV or PO, if symptom duration &gt; 7 days; case by case decision for children and pregnant women pending additional results and with the respective specialists</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider start remdesivir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 200 mg loading dose (IV, within 30 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 100 mg once daily for day 2 to day 10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*treatment duration should be at least 5 days with a maximum of 10 days.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider lopinavir/ritonavir 400/100 mg (= 2 tablets of 200/50 mg) BID for 14 days; as second choice if remdesivir unavailable and provided it can be</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

* Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,…), diabetes, coronaopathy, chronic obstructive pulmonary disease, arterial hypertension

² Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,…), diabetes, coronaopathy, chronic obstructive pulmonary disease, arterial hypertension
Confirmed COVID-19 Critical disease

- 1 of the following:
  - Acute Respiratory Distress Syndrome
  - Sepsis
  - Altered consciousness
  - Multi-organ failure

Optimal supportive care in ICU
Mechanical ventilation
Specific prevention & treatment of ARDS
Track secondary bacterial and opportunistic (Aspergillus) infections
Prevention of sub-sequent lung fibrosis

Consider Dexamethasone 6 mg IV once a day for 10 days (considering the usual contra-indications and waiting for the trial publication); case by case decision for children and pregnant women pending additional results and with the respective specialists

Consider Remdesivir (compassionate use or within trial)
- 200 mg loading dose (IV, within 30 min)
- 100 mg once daily for 2 to 10 days

*treatment duration should be at least 5 days with a maximum of 10 days.

NB: tocilizumab and other interleukins (6 or 1) blockers:

See row above
methasone, tocilizumab, anakinra, otlimab, Siltuximab etc... in this most critical group

Clinical experience and small observational studies suggest a favorable effect in the most critical patients suffering from persistent and overwhelmed inflammation resembling cytokine release syndrome (CRS). At this moment however, this class of drugs should only be used in clinical trials.

4. Clinical trials in Belgium

For an overview of all currently running clinical trials in Belgium, you can search on https://databankklinischeproeven.be (fill in covid-19 as search term in the ‘medical condition/pathology’ field). Additional trials are currently being set up in Belgium. The table below briefly summarizes only ONGOING trials (already recruiting).

Table 3: Belgian COVID-19 Clinical Trials

<table>
<thead>
<tr>
<th>PROTOCOL CODE / EudraCT n°</th>
<th>STUDY TYPE</th>
<th>INVESTIGATED PRODUCTS</th>
<th>PATIENT PROFILE</th>
<th>PRINCIPAL INVESTIGATOR/COORDINATING CENTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>COV-AID 2020-001500-41</td>
<td>Multicentric, randomized, factorial design, interventional study</td>
<td>Six arms: Anakinra (anti-IL1), Siltuximab (anti-IL6), Tocilizumab (anti-IL6) in monotherapy, double or single combinations; standard of care (SoC)</td>
<td>COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome.</td>
<td>Bart Lambrecht / UGent</td>
</tr>
<tr>
<td>SAR PAC 2020-001254-22</td>
<td>Multicentric, randomized, open-label, interventional study</td>
<td>2 arms: Sargramostim (recombinant GM-CSF) vs SoC</td>
<td>Acute hypoxic respiratory failure of COVID-19 patients</td>
<td>B. Lambrecht / Ugent</td>
</tr>
<tr>
<td>DAWN – azithro 2020-001614-38</td>
<td>Multicentric, randomized, open-label, adaptive, proof-of- concept clinical trial</td>
<td>2 arms: Azithromycin vs SoC (other arms can be included further)</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>DisCoVeRy 2020-000936-23</td>
<td>Multicentric, randomized, open-label, adaptive clinical trial</td>
<td>2 arms: HCQ, lopinavir/ritonavir, lopinavir/ritonavir + lopinavir/ritonavir</td>
<td>COVID-19 PCR confirmed</td>
<td>M. Hites / Hôpital Erasme</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Results</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>HCQ arm suspended</strong></td>
<td>interferon: remdesivir; SoC</td>
<td>hospitalized patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DAWN-plasma</strong> (No IMP, therefore no EudraCT number)</td>
<td>Open-label randomized Multicenter Adaptive design</td>
<td>2arms: convalescent plasma vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>G. Meyfroidt/ UZ Leuven</td>
</tr>
<tr>
<td><strong>REM-P-CAP</strong> 2015-002340-14</td>
<td>Randomized, embedded, multifactorial, adaptive platform trial for community acquired pneumonia, amended for COVID-19</td>
<td>Antiviral therapy: No vs Kaletra</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZA, AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent</td>
</tr>
<tr>
<td><strong>DAWN-antico</strong> 2020-001739-28</td>
<td>Randomized, open-label, adaptive, proof-of-concept clinical trial</td>
<td>3 arms: High prophylactic LMWH +/- anakinra*; Apronin (antifibrinolytic) +/- anakinra*; standard dose of LMWH * anakinra only for patients in hyperinflammatory stage</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td><strong>Biophytis – BIO101</strong> 2020-001498-63</td>
<td>Adaptive design phase 2 to 3, randomized, double-blind, multicentre clinical trial</td>
<td>2 arms: BIO101 (activator of Mas-receptor of the renin-angiotensin system) vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UCL Namur St Elisabeth AZ St Maarten (Mechelen)</td>
</tr>
<tr>
<td><strong>ZILU-COV</strong> 2020-002130-33</td>
<td>Prospective, randomized, open-label, interventional clinical trial</td>
<td>2 arms: Zilucoplan (inhibitor of complement protein C5) vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>B. Lambrecht/UZ Gent</td>
</tr>
<tr>
<td><strong>OSCAR (GSK)</strong> 2020-001759-42</td>
<td>Randomized, double-blind, placebo-controlled clinical trial</td>
<td>2 arms: Otilimab (anti-GM-CSF) vs SoC</td>
<td>Patients with severe pulmonary COVID-19 related disease</td>
<td>GSK</td>
</tr>
</tbody>
</table>

**Terminated trials**
- Antivirals for COVID-19 2020-001243-15 (itraconazole)
- COVIDAM 2020-001417-21
- SANOFI 2020-001269-3
5. Annexes

Annex 1: Procedures

Emergency Compassionate use procedure (as stated in art 107/1 (link))

At this moment the availability of remdesivir is very restricted (long delay for supply) and very strict criteria and selection of treatment centers by Gilead apply.

Compassionate use for pregnant women and children: request on https://rdvcu.gilead.com/

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. The notification should include the following information:

- The name of the sponsor
- The name of the treating physician
- A sworn statement from the physician that the informed consent was obtained in accordance with the law of 22 August 2002 on patient rights
- The indication
- The motivation that without appropriate treatment, it is expected that the patient’s death occurs in a short delay or that the risk for the consequences of the absence of treatment is greater than the risk for the consequences of starting the treatment is included. Please discuss the indication of the patient as well as the previous treatments that the patient received, the unmet need and the benefit/risk balance of treatment along with the urgency for this treatment.

Import (as stated in art 105 (link))

Chloroquine base can be imported from NL (A-CQ 100) or FR (Nivaquine) with a prescription and a doctor’s statement (see bijlage VI van de geneesmiddelenwet, annexe VI de la loi sur les médicaments) directed to the hospital pharmacy. However availability is subject to change.

If you have problems obtaining the medicinal products in this guideline, please contact coronashortages@fagg-afmps.be.
Annex 2: Safety profiles

Please download this document (rather than visualize in Web browser) to enable these links to pdf documents to work

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

Annex 3: Precautions of use for hydroxychloroquine that have been included in previous versions of the guideline (when off-label hydroxychloroquine was considered as a treatment options)

Contra-indications

- Known allergy to the drug

Precautions hydroxychloroquine:

- QTc > 450 msec
- Hypokalemia/hypomagnesemia
- drug interaction; check at http://www.covid19-druginteractions.org (Liverpool) Interaction potential of hydroxychloroquine is likely the same as chloroquine
- Known G6PD deficiency
- Myasthenia gravis
- Porphyria
- Retinal pathology
- Epilepsy
- Uncontrolled diabetes
- Renal failure
- Cirrhosis

NB: pregnancy is not a contra-indication as such (large safety experience with chloroquine); see risk/benefit balance

NB: Sanofi has requested that adverse events related to hydroxychloroquine are reported to Pharmacovigilance.Belgium@sanofi.com

NB: no sufficient evidence supporting the association of azithromycin with hydroxychloroquine at this moment (outside clinical trials)
References


