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

06 May 2020; Version 8
Links to guidelines on oxygen therapy added 20 May 2020

1. Preliminary note

This document has been revised on the 06th of May 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-amps.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). 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 possibly 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 in this guideline.

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 used¹, 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>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>(available in Belgium only in compassionate use or within trials)</td>
<td>[6,7]</td>
<td>[6–9]</td>
<td>[10]</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>NCT04252664 [suspended]</td>
<td></td>
<td>NCT04257656</td>
<td>Terminated: no survival benefit could be demonstrated (see details below) [12]</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)
Chloroquine phosphate  

- 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>Effect</th>
<th>Not studied</th>
<th>Not studied</th>
<th>Not studied</th>
<th>Investigated only in &quot;Solidarity (WHO)&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>[13,14]</td>
<td>[15]</td>
<td>[10]</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

**Note:** FDA approval on 29/04 for emergency use, **BUT NO DATA published so far**

Hydroxychloroquine (Plaquenil®); 

- Used for lupus, rheumatoid arthritis 

<table>
<thead>
<tr>
<th>Effect</th>
<th>Not studied</th>
<th>Not studied</th>
<th>Not studied</th>
<th>Ongoing for SARS-CoV-2 NCT04261517</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-?</td>
<td>[17]</td>
<td>[18]</td>
<td>[19]</td>
<td>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) [19]; Under investigation in the Solidarity (WHO), DisCoVeRy (INSERM) and Recovery (UK) trials, at high dosages (see text)</td>
</tr>
</tbody>
</table>

Lopinavir /ritonavir (Kaletra®); 

- Used in HIV infection 

<table>
<thead>
<tr>
<th>Effect</th>
<th>Not studied</th>
<th>Not studied</th>
<th>Not studied</th>
<th>Weak efficacy for SARS-CoV-1; associated with ribavirin &amp; corticosteroids [22]; Negative results for SARS-CoV-2 in both a RCT and observational study</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-</td>
<td>[20–22]</td>
<td>[23]</td>
<td>[8,24]</td>
<td>SARS-CoV-2 protease inhibition?</td>
</tr>
</tbody>
</table>
### 2. Therapeutics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Use</th>
<th>Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favipiravir</strong></td>
<td>Used in Japan against influenza</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>At higher dosage than for influenza</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shorter viral clearance time and improved radiological evolution compared to lopinavir / ritonavir (non-randomized)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Inhibition of the activity of RNA dependent RNA polymerase (RdRp)</td>
<td>++</td>
</tr>
</tbody>
</table>

| **Camostat**  | Used in Japan for reflux esophagitis and pancreatitis                        | ++      |
|               | Inhibition of TMPRSS2, a cellular serine protease, that primes SARS-CoV-2 Spike (S) protein for cell-entry | ++      |

Note: Many other antiviral/immunological treatments have been/are being investigated, including 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.

The selection of the six drugs (in Table 1) relies on demonstrated (in vitro) efficacy, possible availability and known safety profile. 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, pharmacetic inhibition of virus replication should be administered as early as possible after symptom onset [32,33].
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 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 in patients with co-morbidities and co-medication. For this reason, we strongly recommend that its use in suspected/confirmed COVID-19 be restricted to hospitalized patients.

A recent article suggests that hydroxychloroquine (drug marketed in Belgium as Plaquenil®) is more potent than chloroquine *in vitro* (EC50=0.72 µM), so that lower dosages (than initially recommended) could be used [18]. It has also a better safety profile than chloroquine (larger therapeutic window). Based on these considerations and some preliminary results from a small clinical study (see below), hydroxychloroquine was preferred over chloroquine as adjunctive treatment since the first release of this guidance (13th of March, 2020), taking also into account that therapy would be likely required mostly in older patients and/or in case of severe disease (at least for the moment). This study, which has meanwhile been published, suggests that SARS-CoV-2 positivity in nasopharyngeal secretions (measured by RT-PCR) is significantly decreased at day 6 after inclusion (i.e. day 10 after symptom onset) in hydroxychloroquine-treated COVID-19 patients (n=26) versus patients who received supportive care only (n=16 external controls). However, several major limitations (small sample size, non-homogeneous compared groups [differences in viral loads, in number of days since onset of symptoms and in quality of follow-up], and rather late HC administration, close to the expected time of viral clearance), make these observations rather weak [19]. In general, the current evidence therefore does not imply a translation of (hydroxy)chloroquine *in vitro* activity to clinically relevant outcomes. Many previous clinical studies of these compounds in other virus infections showed disappointing results. Results of ongoing clinical trials of chloroquine/ hydroxychloroquine efficacy in the treatment of hospitalized COVID-19 patients are eagerly awaited (Solidarity, Discovery, Recovery,...), before STRONG recommendations can be provided for or against the use of these drugs. Of note high doses of hydroxychloroquine (up to 8,800 mg over 10 days) are used in these three trials. In the same line, it is not possible at this stage to recommend outpatient use of hydroxychloroquine for patients with mild COVID, including those at highest risk of complications (risk of toxicity versus uncertain benefit). Finally, although promoted by some groups, there is no sufficient evidence to recommend the combination of azithromycin with hydroxychloroquine outside clinical trials (no clear data on antiviral activity of azithromycin, and risk of increased cardiac toxicity, as already reported in France, where this combination is very “popular”) [34].

Pending trial results, and based on limited pharmacokinetic data and a risk/benefit balance, administration of “low-dose” hydroxychloroquine sulphate has 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. In case of renal impairment, taking into account the paucity of PK data, it is recommended to administer the same loading dose (D1) but to decrease the D2-D5 dose to 50% if GFR between 10 and 30 ml/min, and to 25% if GFR < 10 ml/min or dialysis (very weak evidence). Evidence is weak, so that hydroxychloroquine should NOT be considered as standard of care, and use in clinical studies/trials should be preferred. It is however currently considered as a reasonable treatment option for hospital clinicians who have no access to study drugs.
contrast, in the ambulatory setting, the risk/benefit balance is less favorable (risk of toxicity in case of unsupervised hydroxychloroquine administration), and full treatment in outpatients should be restricted to clinical studies with adequate follow-up. Because of the long elimination half-life of the drug (32–50 days), the duration of treatment should not exceed 5 days to avoid accumulation of hydroxychloroquine concentrations in plasma and tissues, and associated increased risk of toxicity, and because there is no in vitro evidence that longer courses improve drug activity on SARS-CoV-2.

QTc > 500msec, myasthenia gravis, porphyria, retinal pathology, epilepsy and uncontrolled diabetes are contra-indications for the CHRONIC use of hydroxychloroquine (for which the indication has been granted in the SmPC). However, for the very short-term administration as proposed here for COVID-19, these conditions have been listed as “precautions of use”. Similarly, considering the precaution concerning G6PD deficiency, we do not recommend a test for G6PD deficiency in all non-European patients. There is no single reported case of acute hemolysis after short courses of (hydroxy)chloroquine. If hospitals consider testing patients, this should not delay the start of the treatment (the test is not widely and immediately available). Because probably patients with G6PD deficiency are aware of their disease, this should be asked at time of admission, and patients specifically followed-up for this adverse event. Cases of hemolysis should be reported through the usual canals (see elsewhere). On a final note, because availability of hydroxychloroquine might become problematic at some moments, instructions for the use of chloroquine have also been provided in this guidance, but more caution is required.

The risk of serious adverse events associated with chloroquine and hydroxychloroquine has been 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 75 cases of QTc prolongation have been reported with hydroxychloroquine, 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 hypokaliema/hypomagnesemia (n=4 for the latter, less known factor that may cause QTc prolongation). Based on these new findings, we recommend QTc to be monitored by daily ECG if it is initially above 450 msec, and to check for magnesium concentration in case of underlying conditions that might cause depletion.

- **Lopinavir/ritonavir** (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). Lopinavir/ritonavir can still be therefore considered a second choice for the moment, when hydroxychloroquine is contraindicated, but only if this treatment could be administered early in the course of the disease (within 12 days after symptoms onset). We consider this treatment as futile if administered later on.

- **Remdesivir** seems promising in vitro as well as in one non-randomized observational studies [35], but availability remains a key issue in Belgium (very restricted compassionate use, to the most severe patients but with numerous exclusion criteria [see Table 2]. At the time of writing this version, no peer-reviewed RCT demonstrating any clinical benefit has been published, although 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). In contrast, a trial in China 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]. In addition to being underpowered, it appears that the study allowed patients in the control arm to be treated with various antivirals in the different study hospitals. The results are therefore inconclusive, and large ongoing RCTs (Solidarity, DisCoVeRy, additional US trials) should provide soon a definitive answer.

- **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 [36]. 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) [37]. 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 [27]. 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 a repurposed drug after it has been shown to reduce SARS-CoV-2 infection of primary human lung cells (Calu-3 cell line) in vitro [30]. 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 [38,39]. 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. 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 [40]. Administration of convalescent plasma must only be considered within the multicentric study DAWN-plasma about to be launched (coordinating center: KUL with 14 collaborating centers in Belgium). Both Rode 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.

In accordance with WHO interim guidance [41] and a Correspondence in the Lancet [42], corticosteroids are not recommended as a systemic adjunctive treatment. Low dose dexamethasone is a treatment option which is however being investigated in one of the Recovery study arms. Regarding ACE inhibitors or ARBs, there is currently no evidence from clinical or epidemiological studies that establishes a link between their use and worsening of COVID-19. A recent large cohort study has not found any impact of ACE/ARB use on mortality of patients hospitalized with COVID-19 in different countries [43]. 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).

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. 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. 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 - 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 [44]. No transplacental transmission/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 [45,46]. 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 [47]. 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) [48,49]. 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) [50]. 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 (favorable for (hydroxy)chloroquine or lopinavir/ritonavir, for which large experience exists), 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 3) [46]. 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) [51]. 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 [52]. 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 [53–55]. 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 [51,56,57]. 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, oral anticoagulant treatment (prior to admission) is to be replaced 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 working

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 been constituted to develop guidelines on the treatment of COVID-19 patients in ambulatory care and in nursing homes. These will be communicated as soon as finalized.

Table 2: Supportive care & 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 antiviral therapy</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of COVID-19</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>Mild-to-moderate symptoms (no dyspnea)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ex. Hospitalization for social-related reasons</td>
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<td></td>
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</tbody>
</table>

Case by case discussion, if possible with an Infectious Disease Specialist, to initiate an empirical antiviral therapy, based on the potential delay to obtain results (antiviral therapy is expected to be more efficient if started early in the course of the disease), or on other considerations (high risk of secondary complications).

If decision to treat empirically (in hospitals), follow the treatment options as described for “CONFIRMED CASES”.

Confirmed COVID-19

- Mild-to-moderate disease (no O2 requirement/no evidence of pneumonia)
- Risk group

Symptomatic treatment

Consider start hydroxychloroquine
(Plaquenil®) IF NO CONTRA-INDICATION AND NO ACCESS TO STUDY DRUGS OR TRIALS

- 400 mg at suspicion/diagnosis;
- 400 mg 12 h later
- Followed by 200 mg BID up to Day 5

NB: when patients improve while on hydroxychloroquine there is no need for delayed hospital discharge, and the 5-day course can be completed at home. The hospital should provide the necessary tablets upon discharge. See guideline below for monitoring

- Hydroxychloroquine

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

2 Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,…), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension
If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 or chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 500mg BID up to day 5.

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

NB: use with caution if renal impairment, taking into account the paucity of PK data; keep the same loading dose (D1) but decrease the D2-D5 dose to 50% if GFR between 10 and 30 ml/min, and to 25% if GFR < 10 ml/min or dialysis (very weak evidence)

Perform ECG daily if initial QTc 450-500 msec, and biochemistry (including potassium level) according to underlying disease

Avoid quinolones and macrolides if possible, or monitor closely the QT if these antibiotics are needed

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)

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**Confirmed COVID-19 Severe disease**

≥ 1 of the following:
- Respiratory rate ≥30/min (adults); ≥40/min (children < 5)
- Blood oxygen saturation ≤93%
- PaO2/FiO2 ratio <300

| **Optimal supportive care in hospital** | **Consider start hydroxychloroquine** (Plaquenil®) if no contraindication and no access to study drugs or trials |
| - Provide O2 | - 400 mg at diagnosis; |
| - Administer prophylactic LMWH if not | - 400 mg 12 h later |
| | - Followed by 200 mg BID up to Day 5 |

*NB: when patients improve while on hydroxychloroquine*

See row above for contraindications and precautions regarding hydroxychloroquine
- **Lung infiltrates**
  >50% of the lung field within 24-48 hours

  contra-indicated

  Consider carefully antibiotics or antifungals according to local epidemiology

  **there is no need for delayed hospital discharge, and the 5-day course can be completed at home. The hospital should provide the necessary tablets upon discharge.**

  **NB: If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 OR chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 500mg BID up to day 5**

  Consider **lopinavir/ritonavir 400/100 mg (= 2 tablets of 200/50 mg) BID for 14 days** as second choice ONLY if hydroxychloroquine/chloroquine contra-indicated and provided it can be administered within 12 days after symptoms onset (check also drug interaction!); or in children < 10 kg (after IDS advice)

<table>
<thead>
<tr>
<th>Confirmed COVID-19 Critical disease</th>
<th>Optimal supportive care in ICU</th>
<th>Consider Remdesivir (compassionate use or within trial)</th>
<th>Remdesivir:</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 of the following:</td>
<td>Mechanical ventilation</td>
<td>- 200 mg loading dose (IV, within 30 min)</td>
<td>At this moment very restricted availability of remdesivir in Belgium (long delay for supply; very strict criteria and <strong>with priority to some centers selected by Gilead</strong>)</td>
</tr>
<tr>
<td>- Acute Respiratory Distress Syndrome</td>
<td>Specific prevention &amp; treatment of ARDS</td>
<td>- 100 mg OD for 2 to 10 days</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>- Sepsis</td>
<td>Track secondary bacterial and opportunistic (Aspergillus) infections</td>
<td>If remdesivir unavailable: Consider <strong>(hydroxy)chloroquine</strong>, crushed in nasogastric tube, at the same dosage and monitoring as above; replace with remdesivir if it becomes available</td>
<td><strong>Adult and pediatric patients 12y and &gt;40kg in ICU</strong></td>
</tr>
<tr>
<td>- Altered consciousness</td>
<td></td>
<td>However, since the clinical efficacy of (hydroxy)chloroquine is not</td>
<td>+ confirmation SARS-Cov-2 by PCR</td>
</tr>
<tr>
<td>- Multi-organ failure</td>
<td></td>
<td></td>
<td>(or known contact with confirmed cases, with PCR pending)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exclusion criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Evidence of MOF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Need of inotropic agents</td>
</tr>
</tbody>
</table>
Prevention of sub-sequent lung fibrosis

NB: ongoing studies with dexamethasone, tocilizumab, ...
in this most critical group demonstrated, caution is required in severe cases with kidney/liver/cardiac failure, and abstention in such situations may be preferred (see above)

**NB: tocilizumab and other interleukins (6 or 1) blockers:**
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 or within Belgian/international cohort studies if possible. The drug could be considered on an individual basis in patient with persistent inflammation (i.e. elevated IL-6, CRP, D Dimers, ferritin,..) and ARDS requiring mechanical ventilation without evidence of bacterial superinfection/sepsis.

- Creatinine clearance < 30 ml/min, dialysis, or hemofiltration
- Transaminases > 5X ULN
- Not included in any other CT of experimental agent treatment for COVID-19

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

Still limited information on drug interaction is available. Risk-benefit assessment should be made individually. Close monitoring of remdesivir toxicity or diminished efficacy of concomitant drug is recommended. Check also for interaction with remdesivir at http://www.covid19-druginteractions (Liverpool).
4. Clinical trials in Belgium

For an overview of all currently running clinical trials in Belgium, you can search on [https://databankclinischeproeven.be](https://databankclinischeproeven.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, Siltuximab, Tocilizumab in monotherapy, double or single combinations; standard of care</td>
<td>COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome.</td>
<td>Bart Lambrecht / UGent</td>
</tr>
<tr>
<td>Antivirals for COVID-19</td>
<td>Monocentric, randomized, open-label, adaptive, proof-of-concept clinical trial</td>
<td>2 arms: Itraconazole vs standard of care</td>
<td>COVID-19 PCR confirmed severe hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>SARPAC 2020-001254-22</td>
<td>Multicentric, randomized, open-label, interventional study</td>
<td>2 arms: Sargramostim (Leukin) vs standard of care</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 standard of care (other arms can be included further)</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>SANOFI 2020-001269-35</td>
<td>Multi-country, multicentric, randomized, double-blinded, placebo-controlled study</td>
<td>2 arms: Hydroxychloroquine vs placebo</td>
<td>Outpatient adults with COVID-19</td>
<td>UCLouvain / SANOFI</td>
</tr>
<tr>
<td>COVIDAM 2020-001417-21</td>
<td>Open-label randomized controlled trial</td>
<td>2 arms: Hydroxychloroquine vs symptomatic care</td>
<td>Outpatient adults with COVID-19</td>
<td>E. Bottieau / ITG</td>
</tr>
</tbody>
</table>
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-ifmps.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-ifmps.be.
Annex 2: Safety profiles

Safety profile remdesivir.pdf  Safety profile chloroquine.pdf  Kaletra RCP.pdf  Kaletra SKP.pdf  Plaquenil RCP.pdf

Plaquenil SKP.pdf  Roactemra RCP.pdf  Roactemra SKP.pdf

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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: Thorough evaluation for hydroxychloroquine

Optional tool for use in monitoring patients on hydroxychloroquine
(Version 02 Apr 2020: modifications in this tool since previous update have been highlighted)

Recommendation.pdf

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References


