1. Preliminary note

This document has been revised on the **07th of June 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-amfps.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 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><em>In vitro activity</em></th>
<th><em>In vivo activity</em> (animal models)</th>
<th>Clinical studies (non-exhaustive)</th>
<th>Mechanism of action</th>
</tr>
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<tbody>
<tr>
<td>Remdesivir / GS5734</td>
<td>+++ [6,7]</td>
<td>+++ [6–9]</td>
<td>NCT04252664 (suspended)</td>
<td>Interactions with viral polymerase [6,9]</td>
</tr>
<tr>
<td>(available in Belgium only in compassionate use or within trials)</td>
<td>+++ [10]</td>
<td>+++ [11]</td>
<td>NCT04257656 Terminated: no survival benefit could be demonstrated (see details below) [12]</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)
<table>
<thead>
<tr>
<th>Chloroquine phosphate (CQ)</th>
<th>+++</th>
<th>++</th>
<th>++</th>
<th>+/-</th>
<th>Not studied</th>
<th>Investigated only in Solidarity (WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(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</td>
<td>[14,15]</td>
<td>[16]</td>
<td>[10]</td>
<td>[17]</td>
<td></td>
<td>Very large retrospective non-randomized study showing no survival benefit and even increase in mortality in patients treated with CQ or HCQ in particular if associated with macrolide (compared to controls with no or other treatments) [18] (\rightarrow) RETRACTED</td>
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</table>

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<thead>
<tr>
<th>Hydroxychloroquine (HCQ) (Plaquenil®); Used for lupus, rheumatoid arthritis</th>
<th>+/-</th>
<th>Not studied</th>
<th>+++</th>
<th>Not studied</th>
<th>Not studied</th>
<th>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) [21] Under investigation in the Solidarity (WHO), DisCoVeRy (INSERM) and Recovery (UK) trials, at high dosages (see text)</th>
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<tbody>
<tr>
<td></td>
<td>[19]</td>
<td>Not studied</td>
<td>[20]</td>
<td></td>
<td></td>
<td>RECOVERY stopped enrolling patients in hydroxychloroquine (9600 mg x 10 days) arm: no benefit in patients hospitalized with COVID-19 (June 5th) (\rightarrow) See above [18]</td>
</tr>
</tbody>
</table>

Faster recovery demonstrated in a preliminary report of the RCT NCT04280705 (results on mortality still pending) [13]
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effectiveness</th>
<th>Safety Profile</th>
<th>Use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir /ritonavir (Kaletra®)</td>
<td>+/-</td>
<td>Not studied</td>
<td>Not studied</td>
<td>+/-</td>
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<tr>
<td>Used in HIV infection</td>
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Favipiravir

Used in Japan against influenza

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<thead>
<tr>
<th>Effectiveness</th>
<th>Safety Profile</th>
<th>Use</th>
<th>Notes</th>
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<tbody>
<tr>
<td>++</td>
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<tr>
<td></td>
<td>(at higher dosage than for influenza)</td>
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Camostat

Used in Japan for reflux esophagitis and pancreatitis

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<tr>
<th>Effectiveness</th>
<th>Safety Profile</th>
<th>Use</th>
<th>Notes</th>
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<tr>
<td>++</td>
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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.

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, pharmaceutic inhibition of virus replication should be administered as early as possible after symptom onset [34,35].

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 in patients with co-morbidities and co-medication.

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 [20]. 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 emergency 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. The initial clinical study that suggested a shorter viral shedding in hydroxychloroquine-treated patients (compared to controls) had however several major limitations (small sample size, non-homogeneous compared groups, and rather late HCQ administration) making it a very weak evidence base [21]. Meanwhile several major randomized controlled trials (RCTs) have been launched, that evaluate the efficacy and safety of chloroquine/ hydroxychloroquine in the treatment of hospitalized COVID-19 patients (Solidarity, Discovery, Recovery,...) Of note high doses of hydroxychloroquine (up to 8,800 mg over 10 days) are being explored in these three trials.

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 (with dose adaptation in case of renal impairment, see Table 2) 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 [36].
Several studies could not demonstrate any independent benefit of hydroxychloroquine use compared to controls [37–40]. However, in addition to their retrospective design, they were underpowered to assess mortality outcome and many “control” patients were exposed to different alternative antivirals (often in combination). The analysis of a much larger multinational registry (96,000 admitted COVID-19 patients, the vast majority with rather mild disease, including about 15,000 exposed to CQ or HCQ alone or in combination with macrolide) did not find any benefit in the CQ/HCQ groups after adjustment, and even found an increased mortality and higher frequency of ventricular arrhythmia [18]. There have however been concerns expressed by the global scientific community with regards to this article, concerning both content and methodology. (Article retracted by authors on the 4th of June). Authors were unable to complete an independent audit of the data underpinning their analysis. As a result, they have concluded that they “can no longer vouch for the veracity of the primary data sources. This article had considerable impact, including the temporary suspension of the HCQ arms of the DisCoVery and SOLIDARITY trials. It has also impacted on clinical trials in Belgium, cfr Table 3. After evaluation of available mortality data, the continuation of all arms of the Solidarity Trial, including hydroxychloroquine, was endorsed on the 3 June 2020. The expert panel reviewing the interim results of DisCoVery have also recommended the continuation of the study as originally planned, and HCQ arm may be resumed pending authorization from the competent authorities. In contrast, Recovery trial has stopped enrolling patients on the 5th of June after finding no beneficial effect of hydroxychloroquine (9600 mg over 10 days) in patients hospitalised with COVID-19. Publication of the preliminary results of the study are awaited link.

Overall, based on these recent observational findings which all consistently point to an absence of benefit related to hydroxychloroquine use, it has been decided not to recommend its off-label use for COVID-19 in Belgium anymore, except within ongoing clinical registered trials after careful reassessment of the study-related risk/benefit. New trials aimed at evaluating this drug should also take the potential risks into prudent consideration.

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** (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) [28]. 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 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 [41]) 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). A 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]. Besides to be 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.

Meanwhile, a preliminary report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US has been made public, showing a faster recovery in remdesivir-treated COVID-19 patients requiring oxygen compared to patients given placebo (11 days instead of 15 days). No data are available yet on mortality or other clinical endpoint. Such an effect was not seen in patients not requiring supplemental oxygen and in patients requiring mechanical ventilation. On Monday 11th of May, the European Medicines Agency (EMA) recommended expanding the compassionate use of remdesivir so that more patients with severe COVID-19 can be treated. EMA is currently evaluating the data in the context of a rolling review of remdesivir. When the evaluation is complete, EMA will make a recommendation on whether or not remdesivir should receive a marketing authorization.

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 [42].

- **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 [43]. 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) [44]. 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 [29]. 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 [32]. 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 [45,46]. 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 [47]. 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.

In accordance with WHO interim guidance [48] and a Correspondence in the Lancet [49], 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 [50] (Article retracted by authors on 4th of June: “all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor, we are unable to validate the primary data sources underlying our article”). 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 [51]. 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 [52,53]. 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 [54]. 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) [55,56]. 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) [57]. 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) [53]. 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) [58]. 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 [59]. 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 [60–62]. 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 [58,63,64]. 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 – wwwebp-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 ebpracticeney database, so that they can also be quickly consulted by general practitioners from their medical records and by all other primary care workers.
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<thead>
<tr>
<th>Clinical category</th>
<th>Supportive Care</th>
<th>Additional antiviral therapy</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspection 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>Suspection of COVID-19</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>Confirmed COVID-19</td>
<td>Symptomatic treatment</td>
<td>Consider hydroxychloroquine (Plaquenil®) ONLY WITHIN CLINICAL STUDIES/TRIALS, preferably at the following dosage: 400 mg at suspicion/diagnosis; 400 mg 12 h later; Followed by 200 mg BID up to Day 5</td>
<td></td>
</tr>
</tbody>
</table>
| Hydroxychloroquine | (for use in Clinical trial). General precautions:  
  **Contra-indications**  
  > Known allergy to the drug  
  > Known G6PD deficiency  
  > Myasthenia gravis  
  > Porphyria  
  > Retinal pathology  
  > Epilepsy  
  > Uncontrolled diabetes  
  NB: pregnancy is not a contra-indication as such (large safety experience with chloroquine); see risk/benefit balance |

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

3 Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,…), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension
<table>
<thead>
<tr>
<th>Confirmed COVID-19 Severe disease</th>
<th>Optimal supportive care in hospital WARD (or ICU)</th>
<th>Consider start remdesivir (compassionate use or within clinical trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 of the following:</td>
<td></td>
<td>• 200 mg loading dose (IV, within 30 min)</td>
</tr>
<tr>
<td>➢ Respiratory rate ≥30/min (adults); ≥40/min (children &lt; 5)</td>
<td>Provide O2</td>
<td>• 100 mg once daily for day 2 to day 10*</td>
</tr>
<tr>
<td>➢ Blood oxygen saturation ≤93%</td>
<td>Administer prophylactic LMWH if not contraindicated</td>
<td>*In the compassionate-use program of remdesivir, for patients not requiring invasive mechanical ventilation and/or ECMO, a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg for 4 days is recommended. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).</td>
</tr>
<tr>
<td>➢ PaO2/FiO2 ratio &lt;300</td>
<td>Consider carefully antibiotics or antifungals according to local epidemiology</td>
<td>Consider hydroxychloroquine (Plaquenil®) IF NO</td>
</tr>
<tr>
<td>➢ Lung infiltrates &gt;50% of the lung field within 24-48 hours</td>
<td></td>
<td>Remdesivir: At this moment very restricted availability of remdesivir in Belgium (long delay for supply; very strict criteria and with priority to some centers selected by Gilead)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult and pediatric patients 12y and &gt;40kg + confirmation SARS-Cov-2 by PCR (or known contact with confirmed cases, with PCR pending)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Evidence of MOF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Creatinine clearance &lt; 30 ml/min, dialysis, or hemofiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Not included in any other CT of experimental agent treatment for COVID-19</td>
</tr>
</tbody>
</table>

Compassionate use for pregnant women and children: request on https://rdvcu.gilead.com/
REMDESIVIR, AND ONLY WITHIN CLINICAL STUDIES/TRIALS, preferably at the following dosage: 400 mg at diagnosis;
- 400 mg 12 h later
- Followed by 200 mg BID up to Day 5

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 administered within 12 days after symptoms onset (check also drug interaction!); or in children < 10 kg (after IDS advice)

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).

<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>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 of the following:</td>
<td>Mechanical ventilation</td>
<td>- 200 mg loading dose (IV, within 30 min)</td>
</tr>
<tr>
<td>Acute Respiratory Distress Syndrome</td>
<td>Specific prevention &amp; treatment of ARDS</td>
<td>- 100 mg once daily for 2 to 10 days</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered consciousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>Track secondary bacterial and opportunistic (Aspergillus) infections</td>
<td><strong>NB: tocilizumab and other interleukins (6 or 1) blockers:</strong> 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</td>
</tr>
</tbody>
</table>

Remdesivir: See row above for contraindications and precautions regarding remdesivir.
4. Clinical trials in Belgium

For an overview of all currently running clinical trials in Belgium, you can search on [https://databankklinischeproeven.be](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>
<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>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>DisCoVeRy 2020-000936-23</td>
<td>Multicentric, randomized, open-label, adaptive clinical trial</td>
<td>5 arms: HCQ; lopinavir/ritonavir; lopinavir/ritonavir + interferon; remdesivir; standard of care</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>M. Hites / Hôpital Erasme</td>
</tr>
<tr>
<td>Sanofi 2020-001269-35</td>
<td>Multi-country, multicentric, randomized, double-blinded,</td>
<td>2 arms: Hydroxychloroquine vs placebo</td>
<td>Outpatient adults with COVID-19</td>
<td>UCLouvain / SANOFI</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Setting</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>COVIDAM 2020-001417-21 Amendment ongoing</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>
<tr>
<td>DAWN-plasma (No IMP, therefore no EudraCT number)</td>
<td>Open-label randomized multicenter adaptive design</td>
<td>2 arms: convalescent plasma vs standard of care</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>G. Meyfroidt/ UZ Leuven</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-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


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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

References


18 Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet Published Online First: 22 May 2020. doi:10.1016/S0140-6736(20)31180-6 -> RETRACTED


