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

18 September 2020; Version 13

Preliminary note

This document has been revised on the 18 September 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 AFMPS/FAGG (Dr Roel Van Loock at Roel.VanLoock@fagg-afmps.be).

This guidance 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]. In Belgium, during the first epidemic peak, mortality rate of hospitalized patients was 22% [5]. 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 an extensive review on all potential investigational treatments in the pipeline.
We have opted for a document with the following structure:

1. **Executive Summary**, with the current therapeutic recommendations for each category of COVID-19 patients, with indications and precautions (Table 1);
2. **The Belgian recommendations for supportive care and adjunctive antiviral/immunomodulatory treatment for suspected/confirmed COVID-19 cases**, detailing latest evidence and rationale behind this consensus;
3. **A summary of the efficacy data of selected antiviral drugs**, with information on in vitro/in vivo efficacy (Table 2);
4. **An overview of the clinical trials ongoing in Belgium** (Table 3).
5. **Annexes**, covering compassionate use and import procedures, and detailed safety profiles
6. **References**

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**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.

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**1. Executive summary**

**Table 1: 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 therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suspicion of COVID-19</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Mild-to-moderate symptoms (no dyspnea)</td>
<td>Symptomatic treatment</td>
<td>No</td>
</tr>
<tr>
<td>➢ No risk group&lt;br&gt; ex. Hospitalization for social-related reasons</td>
<td></td>
<td></td>
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<tr>
<td><strong>Suspicion or confirmed COVID-19</strong></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>
</tr>
<tr>
<td>➢ Risk group&lt;sup&gt;1&lt;/sup&gt;</td>
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</tbody>
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<sup>1</sup> 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>Clinical category</th>
<th>Supportive Care</th>
<th>Additional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed COVID-19</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe disease</td>
<td>Optimal supportive care in hospital WARD (or ICU)</td>
<td>Dexamethasone 6 mg once a day for up to 10 days (or until hospital discharge if sooner), IV or PO, for which more evidence is available in those with symptom duration &gt; 7 days; case by case decision for children and pregnant women pending additional results and with the respective specialists</td>
</tr>
<tr>
<td>≥ 1 of the following:</td>
<td></td>
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<tr>
<td>➢ Respiratory rate ≥30/min (adults);</td>
<td>Provide 02</td>
<td>Consider start remdesivir, preferentially if symptoms &lt;5 days</td>
</tr>
<tr>
<td>≥40/min (children &lt; 5)</td>
<td>Administer prophylactic LMWH if not contra-indicated</td>
<td>• 200 mg loading dose (IV, within 30 min)</td>
</tr>
<tr>
<td>➢ Blood oxygen saturation ≤93%</td>
<td></td>
<td>• 100 mg once daily for day 2 to day 10*</td>
</tr>
<tr>
<td>➢ PaO2/FiO2 ratio &lt;300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Lung infiltrates &gt;50% of the lung field</td>
<td></td>
<td></td>
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<tr>
<td>within 24-48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Confirmed COVID-19</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical disease</td>
<td>Optimal supportive care in ICU</td>
<td>Dexamethasone 6 mg once a day for up to 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists</td>
</tr>
<tr>
<td>≥ 1 of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Acute Respiratory Distress Syndrome</td>
<td>Mechanical ventilation</td>
<td>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. Ongoing studies with dexamethasone, tocilizumab, anakinra, otilimab, Siltuximab etc...are ongoing in Belgium.</td>
</tr>
<tr>
<td>➢ Sepsis</td>
<td>Specific prevention &amp; treatment of ARDS</td>
<td></td>
</tr>
<tr>
<td>➢ Altered consciousness</td>
<td>Track secondary bacterial and opportunistic (Aspergillus) infections</td>
<td></td>
</tr>
<tr>
<td>➢ Multi-organ failure</td>
<td>Prevention of subsequent lung fibrosis</td>
<td></td>
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</tbody>
</table>

**Precautions of use & additional information**

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

**Dexamethasone**: Usual contraindications

**Remdesivir** (Veklury®): at this moment very restricted availability of remdesivir in Belgium.

- **Contraindications**:
  - Hypersensitivity to active substance(s) or any of excipients
- **Warnings/precautions:**
  - **Hepatic impairment:** Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline.
  - **Renal impairment:** Remdesivir should not be used in patients with eGFR <30 mL/min.
- **Interactions:**
  - Strong inducers of CYP2C8, CYP2D6 and CYP3A4 (e.g. rifampicin) may decrease plasma concentrations and are not recommended.
  - Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.
  - Still limited information on drug 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.org](http://www.covid19-druginteractions.org) (Liverpool).
- Compassionate use for pregnant women & children: request on [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/)

2. Belgian recommendations for supportive care and adjunctive antiviral/immunomodulatory treatment for suspected/confirmed COVID-19 cases.

As summarized in the executive summary table, we recommend that dexamethasone be considered as a standard of care in severe and critical COVID-19 disease. In patients requiring supplemental oxygen, remdesivir may be considered but with a fixed set of key precautions to follow. Background data and rationale behind these recommendations are detailed here. Latest results concerning additional antiviral and immunomodulatory treatments are also covered: chloroquine and hydroxychloroquine, lopinavir/ritonavir, favipiravir, camostat mesylate, azithromycin, interferons, immunomodulatory agents, convalescent plasma and monoclonal antibodies. These treatments are currently only to be prescribed in the context of clinical trials.

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

- **Corticosteroids:** In accordance with WHO interim guidance [6] and a Correspondence in the Lancet [7], 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. In a publication reporting on preliminary results, 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) [8]. 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.
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 has recommended in the version v12 low-dose dexamethasone for admitted patients requiring oxygen, in particular requiring mechanical ventilation and with a symptom onset > 7 days. Following the publication of the RECOVERY results, three other large RCTs evaluating various doses and types of steroids in critical COVID-19 stopped prematurely patient inclusion before reaching the respective target sample sizes, i.e. REMAP-CAP (multicountry) [9], CoDEX (Brazil) [10], and CAPE COVID (France) [11]. The results of RECOVERY, of the last 3 published (“incomplete”) RCTs and of another three ongoing smaller trials were then pooled and meta-analyzed by the WHO REACT working group [12]. The conclusion was robust throughout all trials (n=678 in total versus 1025 in placebo/usual care arm, all critically ill patients): administration systemic corticosteroids in critically ill patients with COVID-19 is associated with decreased 28-day mortality (0.66 (95% CI 0.53-0.82; p<0.001). This association was similar for dexamethasone and hydrocortisone, for higher versus lower doses of steroids, and in admitted patients with fewer or greater than 7 days of symptoms, requiring oxygen either through mechanical ventilation or not. While much works remains on the exact details of implementation into clinical practice, the consistent findings of benefit provide definitive data that corticosteroids should be first-line treatment for critically ill patients with COVID-19 [13].

Nb. Effect of lose-dose and short-course DXM on risk of Strongyloides reactivation is not well known. Nevertheless, for high risk patients, such as originating from Strongyloides endemic area, empirical ivermectin treatment should be considered before, or early during, DXM administration treatment [14].

Remdesivir (RDV) seemed promising in vitro and in non-human primates models [15]. 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 [16]. In this study, there was no effect of RDV on viral load over time in both upper and lower respiratory tract suggesting the absence of antiviral effect.

Meanwhile, a preliminary report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US has been published [17], 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 [18].

A third RCT sponsored by Gilead assessed the role of RDV in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) [19]. The patients (n=584) were randomized 1:1:1 to 10-day course of RDV, 5-day course of RDV and standard of care. Mortality was low (1%). The study found a benefit for a better clinical status with the 5-day course but not the 10-day course. The clinical significance
of this finding remains uncertain as the patients in the 5-day and 10-day courses received almost the same number of doses (5 and 6, respectively).

It is important to highlight that in both the ACTT-1 and Spinner trials, no impact of RDV on viral shedding was reported. In both trials, the median duration of symptoms before enrollment was 9 days, limiting the potential of a significant antiviral effect as it was also observed in the Wang et al trial [16]. In a study performed in rhesus macaque, initiation of RDV very early after infection (12 hours) had better clinical outcome and reduced lung viral replication [15]. This suggests that the impact of RDV would only be expected very early during infection.

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).

As dexamethasone is now considered the standard of care for the hospitalized patients requiring oxygen or on mechanical ventilation, it is important to highlight that there is no data about the concomitant use of dexamethasone and remdesivir.

- 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 [20], 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 comorbidities 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 [21]. It has also a better safety profile than chloroquine (larger therapeutic window).

Several small retrospective studies could not demonstrate any independent benefit of hydroxychloroquine use compared to non-exposed hospitalized patients [22–26]. 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 in-hospital mortality [5,27–29]. No particular safety signals were observed with the use of HCQ (alone) in these large cohorts. 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 (RCT) 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.

Regarding other potential indications, an RCT using HCQ (low-dose) as post-exposure prophylaxis (PEP), showed no prevention of “illness compatible with COVID 19” [40]. This trial had however several limitations such as undocumented treatment adherence and no laboratory confirmation of SARS-CoV-2 infection in 85% of the participants. No serious adverse events were notified. Another RCT by the same group studied early administration of HCQ in mild/ambulatory patients with laboratory-confirmed or symptomatic contacts (n=423), and no substantial symptom reduction was observed in the HCQ arm.
compared to masked placebo [30]. Here again, many participants (about 40%) were not tested. In a well-designed Spanish RCT evaluating early treatment with HCQ in adults with mild disease (n=293), no clinical (shortening of symptoms) nor viral (reduction of shedding) benefits were observed [31]. The results of several other ongoing trials using HCQ are still awaited, including as chemoprophylaxis (PrEP).

Meanwhile, preclinical studies that have been conducted in animal models (hamsters; macaques) and published as preprints have not demonstrated any antiviral effect of HCQ [32–35]. Overall, based on these preclinical observations and the reported trial results it has been decided since beginning of June (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore, except within ongoing clinical registered trials, and after timely interim analysis of the study-related risk/benefit.

- **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 (cfr. Table 2). 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) [36]. On the 4th of July 2020, the WHO announced that the Lopinavir/ritonavir arm was discontinued in the SOLIDARITY trial because of lack of benefit [link]. This arm was also stopped in RECOVERY (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 [37]. 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. No additional evidence has impacted negatively or positively the assessment of LPV/r compared to the previous version (v12).

- **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 [38]. 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) [39]. 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 [40]. Favipiravir has not been selected for these recommendations, as this molecule is not available in Belgium outside clinical trials. Some antiviral effect has been however observed in animal models (hamsters), that need to be further confirmed including in humans [32].

- **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 [41]. Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (eg. NCT04355052 (Israel), NCT04321096 (Denmark)). The drug is not available in Belgium.

- **Azithromycin (AZM)** : this antibiotic shown to have some antiviral and immunomodulatory effect has been promoted by some groups based on observational viral and clinical data [42]. The potential benefit of using AZM alone or with other drugs has not been demonstrated so far. Two large RCTs have explored in Brazil the usefulness of this drug in association with HCQ, both in mild/moderate [43] and severe hospitalized patients [14], and did not find any added-value compared to HCQ alone.

- **Interferons (IFN)** have antiviral effects and modulate the immune response [44]. There are a limited number of case series, case-control trials and three small RCT’s published so far. Hung et al compared
combination therapy including Interferon IFN ß-1b, ribavirin and lopinavir-ritonavir (n=86) vs lopinavir-ritonavir alone (n= 41) in an open label RCT [45]. They found a shortened viral shedding and faster clinical improvement in the IFN-containing arm. Another RCT evaluated IFN ß-1b with or without standard of care including hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir (both groups n=33). They found a faster clinical improvement, in primary outcome; and a decreased mortality at 28d, although the study was probably underpowered for this [46]. The same group also evaluated IFN ß-1a in addition to the same standard of care (n=42) vs standard of care alone (n=39), and could not find any difference in clinical response [47]. Decreased mortality was found in the IFN group. This study has several limitations: >30% of patients had no laboratory-confirmed infection, a very high mortality was observed in the control group and a large drop-out was seen in each study group. Furthermore IFN therapy was associated with more adverse events. A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions [48,49]. Questions remain on optimal dosing, administration, etc. and no RCT is available for this type of administration. Further studies are needed to clarify the role of Interferons in the treatment of COVID-19.

- **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 [50,51]. Roche and Sanofi have announced that trials using Tocilizumab (Roactemera ®) and Sarilumab (Kevzara ®) have failed. Publications are pending. These drugs are intensively investigated including in Belgium (see Table 3). Notably, the COV-AID trials is still recruiting. Inclusion is based on a combination of biological factors (to better select suitable candidates), in contrast with other trials. 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**: Animal studies with SARS-CoV-1 and SARS-CoV-2 infections indicate a protective role of neutralizing antibodies. Several case studies, non-controlled and controlled non-randomized trials and one RCT have been published (as summarized in a Cochrane living review published in July 2020 [52,53]. The 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. This study was however underpowered, furthermore the plasma was administrated late in the course of the disease (median time from symptom onset to randomization: 30 days)[54]. Recently a Dutch RCT was stopped due to the finding of comparable amounts of neutralizing antibodies in patients as in their convalescent plasma, as early as median 10 days after symptom onset, (preprint/non peer-reviewed data) [55]. We only recommend the administration of convalescent plasma within clinical trials in Belgium such as the multicentric study DAWN-plasma and CONFIDENT that are currently ongoing. 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.

- **Monoclonal antibodies**: Dozens of monoclonal antibodies targeting the S protein domains (RBD) have been developed [56]. Some have entered phase II trials this summer. Given the long half-life, a single infusion is generally used and could prevent disease progression [57]. Animal studies with the SARS-CoV-2 model are encouraging [58].
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 [59,60]. 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:

Specialized care and close monitoring for complications is absolutely necessary in COVID-19 pregnant women. A COVID positive patient, if maternal condition allows it, can deliver vaginally. Large organizations like WHO, RCOG and ACOG support the practice of breastfeeding even in the context of active SARS-CoV-2 disease, but with application of necessary preventive measures (mask, nipple cleaning, frequent handwashing). See additional guidance on newborns of COVID-19 positive mothers via the following link. 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) [61]. 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. International guidelines are available, including from NIH, RCOG and WHO guidance.

Note – children:

Specific guidelines are 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.

A consensus guideline on anticoagulation management in COVID-19 positive patients has been published by the Belgian Society on Thrombosis and Haemostasis and available here. Of note, a KCE report on thrombo prophylaxis in COVID-19 diseases concluded that the BSTH management algorithms are of good quality and in agreement with international guidance.
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.
3. Summary of efficacy data of selected antiviral drugs

Table 2: *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 [62]; 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 SARS-CoV-2 (non-exhaustive)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir / GS5734</td>
<td>++</td>
<td>++</td>
<td>NCT04292899: No significant difference in 5-day and 10-day treatment course [18]. Post-hoc analysis showed that patients receiving mechanical ventilation or ECMO may benefit from 10 days</td>
<td>Interactions with viral polymerase [63,66]</td>
</tr>
<tr>
<td>(Veklury®); Limited availability in Belgium</td>
<td>++</td>
<td>++</td>
<td>NCT04257656: Terminated: no survival benefit could be demonstrated [16]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[63,64]</td>
<td>[63–66]</td>
<td>NCT04280705: Faster recovery demonstrated in a preliminary report of the RCT (results on mortality by day 28 pending) [13]. No impact of RDV on viral shedding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[20]</td>
<td>[67]</td>
<td>NCT04292730: Better clinical status with the 5-day course compared with standard of care in non-severe hospitalized cases, but not with the 10-day course. Clinical significance of this finding remains uncertain; No impact of RDV on viral shedding [19].</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>[65]</td>
<td>Under investigation in Solidarity (WHO) and DisCoVeRy (INSERM) trials, but not in Recovery (UK)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Effectiveness</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chloroquine phosphate (CQ)</strong></td>
<td>+++ [68,69] ++ [70] ++ [20] +/- - -</td>
<td>Although in initial Solidarity (WHO) protocol, the trial was only ever pursued with hydroxychloroquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not marketed in Belgium. Available via import or as magistral preparation (500mg CQ = 300mg chloroquine base); Used for malaria</td>
<td></td>
<td>Fusion and uncoating blockade, by lysosomal alkalization [68,69]; Interaction with the ACE2 receptor [68]; “Immuno-modulation”?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydroxy-chloroquine (HCQ) (Plaquenil®)</strong></td>
<td>+/- [72] - +++ [21] -</td>
<td>2020-000890-25: 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) [73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used for lupus, rheumatoid arthritis</td>
<td></td>
<td>Not fully elucidated but assumed to be similar to that of chloroquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lopinavir /ritonavir (Kaletra®)</strong></td>
<td>+/- [74–76] - -</td>
<td>Weak efficacy for SARS-CoV-1; associated with ribavirin &amp; cortico-steroids [76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used in HIV infection</td>
<td></td>
<td>SARS-CoV-2 protease inhibition?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Favipiravir

**Discontinued in the SOLIDARITY because of lack of benefit (press release). Also discontinued in DisCoVeRy.**

<table>
<thead>
<tr>
<th>Status</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>++ *</td>
<td>-</td>
</tr>
</tbody>
</table>

*at higher dosage than for influenza*

---

**ChiCTR2000029600: Shorter viral clearance time and improved radiological evolution compared to lopinavir /ritonavir (non-randomized) [40]**

- NCT04373733 (PIONEER): recruiting
- NCT04349241: Completed, no yet published

### Camostat

**Inhibition of the activity of RNA dependent RNA polymerase (RdRp)[80,81]**

<table>
<thead>
<tr>
<th>Status</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

- NCT04355052 : recruiting
- NCT04321096 : recruiting
- NCT04353284 : recruiting
- NCT04374019 : recruiting

**Inhibition of TMPRSS2, a cellular serine protease, that primes SARS-CoV-2 Spike (S) protein for cell-entry [41]**

### Interferons

**3 RCT’s with small number of patients (see text). Further studies needed**

- ++
- [83]
- [83,44,84]
- [85]
- [86]

---

**Note**: Many other antiviral/immunological treatments have been/are being investigated, including (list not exhaustive) ribavirin, fabiravir, 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 and in Belgium, these trials should ideally be coordinated centrally.

Key points on safety profile are found in Table 1 and an extensive safety profile and/or SmPC of the proposed drugs can be found in Annex 2.
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 (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>SARPAC 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 later)</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: Remdesivir vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>M. Hites / Hôpital Erasme</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 SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>G. Meyfroidt/ UZ Leuven</td>
</tr>
<tr>
<td>REMAP-CAP 2015-002340-14</td>
<td>Randomized, embedded, multifactorial, adaptive platform trial for community acquired</td>
<td>Antiviral therapy: No vs Kaletra Corticosteroid therapy: No vs hydrocortisone 7d</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Patient Population</td>
<td>Location</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>DAWN-antico 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 hyper-inflammatory stage</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>Biophytis – BIO101 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>ZILU-COV 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>OSCAR (GSK) 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>
<tr>
<td>MOT-C-204 (Inotrem) 2020-001504-24</td>
<td>Randomized, double-blind, placebo controlled, adaptive, exploratory clinical study</td>
<td>2 arms: Nangibotide iv (TREM1 inhibitor) vs placebo</td>
<td>Mechanically ventilated patients due to COVID-19 and with features of systemic inflammation</td>
<td>UCL St-Luc, ZOL</td>
</tr>
<tr>
<td>TJT2012 2020-002102-58</td>
<td>Prospective open-label P1/2 clinical trial</td>
<td>Mesenchymal stromal cells</td>
<td>Patients with severe COVID-19 requiring supplemental O2</td>
<td>CHU Liège</td>
</tr>
<tr>
<td>ARGX-117-2001 (ArgenX) 2020-001546-19</td>
<td>First-in-human, open-label P1 clinical study</td>
<td>ARGX-117 iv (Humanized antibody that blocks C2b)</td>
<td>COVID-19 hospitalized patients</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>AT-527 (ATEA Pharmaceuticals) 2020-002869-34</td>
<td>Randomized, double blind,</td>
<td>AT-527 (guanosine nucleotide prodrug)</td>
<td>Moderate COVID-19 patients with CHU St-Pierre, AZ St-Maarten (Mechelen)</td>
<td></td>
</tr>
<tr>
<td>Trial ID</td>
<td>Overview</td>
<td>Design</td>
<td>Arms</td>
<td>Eligibility</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>ABX464-401 (Abivax) 2020-001673-75</td>
<td>Randomized, double blind, placebo controlled, P2/3 trial</td>
<td>ABX464 (antiviral) Vs Placebo</td>
<td>mild-moderate COVID-19 patients with risk factors</td>
<td>UZ Gent, Erasme and CHU Saint-Pierre</td>
</tr>
<tr>
<td>VAC31518COV1001 (J&amp;J) 2020-001483-28</td>
<td>Randomized, double blind, placebo-controlled P1/2a clinical study</td>
<td>7 arms: Ad26COVS1 im (2 dose levels; single or 2-dose schedule) Vs placebo</td>
<td>Healthy volunteers aged 18 to ≤55 years and ≥65 with or without stable underlying conditions</td>
<td>UZ Gent, CHU Liège, ZNA Jan Palfijn, UZ Leuven, UA, ZNA Stuivenbergh</td>
</tr>
<tr>
<td>CV-NCOV-001 (Curevac) 2020-001286-36</td>
<td>First-in-human, partially blind, placebo-controlled, dose escalation P1 clinical study</td>
<td>Different arms: SARS-CoV-2 mRNA vaccine CVnCoV im (3 dose levels; single or 2-dose schedule) Vs placebo</td>
<td>Healthy adults 18 - ≤60</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>TMV-083 (Institut Pasteur) 2020-002973-89</td>
<td>Randomized, placebo-controlled, two center, Phase 1 trial</td>
<td>Different arms: TMV-083 novel measles vector based vaccine candidate (2 dose levels; single or 2-dose schedule) Vs placebo</td>
<td>Healthy volunteers aged 18 to ≤55 years</td>
<td>SGS CPU</td>
</tr>
<tr>
<td>V591-001 (MSD) 2020-003493-46</td>
<td>Randomized, Double-Blind, Placebo-Controlled Phase 1/Phase 2 trial</td>
<td>Different arms: V591 measles based vaccine ascending dose levels; single or 2-dose schedule Vs placebo</td>
<td>Healthy volunteers aged 18 to ≤55 years and ≥60</td>
<td>UZ Gent, SGS CPU, ATC CPU Liège</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)
6. References


35 Hydroxychloroquine in the treatment and prophylaxis of SARS-CoV-2 infection in non-human primates. Published Online First: 6 May 2020. doi:10.21203/rs.3.rs-27223/v1


Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; 11:222.


