

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

07 Avril 2020; Version 7

## 1. Preliminary note

This document has been revised on the 31st of March 2020 to provide support to the diverse groups of Belgian clinicians (general practitioners, emergency physicians, infectious disease specialists, pneumologists, intensive care physicians) who will have to face suspected/confirmed COVID19 cases, during the amplification phase of 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 since the 24<sup>th</sup> of March Dr Ralph Huits, ITG (rhuits@itg.be). It was initially based on the therapeutic protocols elaborated in the two reference institutions (UZA and HSP). It has been revised in fast track by a larger group of physicians and scientists from different specialties/disciplines including experts from ScienSano (Dr Chloe Wyndham-Thomas at Chloe.WyndhamThomas@sciensano.be) and from AMPS/FAGG (Dr Roel Van Loock at Roel.VanLoock@fagg-afmps.be). It is based on the best (but very incomplete) clinical evidence that is currently available, and is purposed to become a “living guideline” which will be regularly updated each time new relevant scientific data will emerge (latest version will always be found via the same [link](#)). 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 (with 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 [1]. Mortality in admitted patients reached 25% (and even 40% in overwhelmed hospitals) in the middle of the epidemic in Wuhan [2]. 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;
- (2) the current therapeutic recommendations for each category of COVID-19 patients, with indications and precautions;

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.

At the time being, the use of investigational or off label medicinal products to treat patients suspected or confirmed COVID 19 should be restricted to hospital use or delivered by hospital teams. We just do not know their clinical efficacy so far. They should therefore not divert health professionals from the optimal supportive care that still provides the highest probability of favorable outcome. Also patients should be each time adequately informed about the uncertain efficacy and respective toxicities of the drugs, and give consent (oral or signed according to the institutions).

Use of off label or investigational antiviral or immunomodulatory drugs should be ideally documented in clinical studies/trials and efforts are undertaken by the KCE to support non-commercial multicentric studies in Belgium. For an overview of all running clinical trials in Belgium, you can search on <https://databankklinischeproeven.be> (fill in covid-19 as search term in the 'medical condition/pathology' field). 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<sup>1</sup>. 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 the drugs selected for treatment of suspected/confirmed COVID-19

Drug	<i>In vitro</i> activity			<i>In vivo</i> activity (animal models)		Clinical studies	Mechanism of action
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	SARS-CoV-1	MERS-CoV		
<b>Remdesivir / GS5734</b> (compassionate use)	+++ [3,4]	+++ [3–6]	+++ [7]	+++ [8]	+++ [5]	Ongoing for SARS-CoV-2 NCT04252664 NCT04257656 NCT04292730 NCT04292899 NCT04280705  Solidarity trial (WHO); DisCoVeRy trial (INSERM); about to start in Belgium	Interactions with viral polymerase  [3,6]

<sup>1</sup> via [www.notifierunefetindesirable.be](http://www.notifierunefetindesirable.be) or [https://www.fagg.be/nl/melden van een bijwerking als gezondheidszorgbeoefenaar](https://www.fagg.be/nl/melden-van-een-bijwerking-als-gezondheidszorgbeoefenaar)

<p><b>Chloroquine phosphate</b></p> <p>(not marketed in Belgium, but available via import; also available as magistral preparation as chloroquine phosphate;</p> <p>500mg chloroquine phosphate = 300mg chloroquine base);</p> <p>Used for malaria</p>	+++ [9,10]	++ [11]	++ [7]	+/- [12]	Not studied	Ongoing for SARS-CoV-2 [13] NCT04286503	Fusion and un-coating blockade, by lysosomal alkalization [9,10]; Interaction with the ACE2 receptor [9]; “immuno-modulation”?
<p><b>Hydroxy-chloroquine</b> (Plaquenil®);</p> <p>Used for lupus, rheumatoid arthritis</p>	+/-? [14]	Not studied	+++ [15]	Not studied	Not studied	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) [16]  Under investigation in the DisCoVeRy trial	Not fully elucidated but assumed to be similar to that of chloroquine
<p><b>Lopinavir /ritonavir</b> (Kaletra®);</p> <p>Used in HIV infection</p>	+/- [17–19]	- [20]	Not studied	Not studied	+/- [5,21]	Weak efficacy for SARS-CoV-1; associated with ribavirin & corticosteroids [19]  Negative results for SARS-CoV-2 in both a RCT and observational study [22,23]; NCT04252885	SARS-CoV-2 protease inhibition ?

**Note** : Many other antiviral/immunological treatments have been/are being investigated, including (list not exhaustive) ribavirin, fabiravir, favipiravir, oseltamivir, darunavir/cobicistat, interferon, mycophenolate, tocilizumab, teicoplanin, convalescent plasma, 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 ideally in a coordinated way in Belgium.

The preliminary selection of the three drugs (in Table 1) relies on (*in vitro*) efficacy, 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.

<b>General guiding principles</b>
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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 [7]. Similar to the use of antiviral therapy in other (unrelated) infections, e.g. oseltamivir in affecting outcomes in influenza infections, pharmaceutical inhibition of virus replication should be administered as early as possible after symptom onset [24,25].

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

- **Chloroquine and hydroxychloroquine** inhibits replication of SARS-CoV-2 *in vitro*. Chloroquine inhibits the virus at concentrations (EC50 = 1.13 µM, equivalent to 360 ng/mL) that cannot be achieved in human plasma [7], but possibly in the intracellular compartment. This drug (not available in Belgium since 2015) has been used for decades (at a total of 25 mg/kg within 3 days) for malaria treatment without any monitoring and side effects, including in pregnant women. However, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages in patients with co-morbidities and co-medication. For this reason, we strongly recommend that its use in suspected/confirmed COVID-19 be restricted to hospitalized patients.

A very recent article suggests that hydroxychloroquine (drug marketed in Belgium as Plaquenil®) is more potent than chloroquine *in vitro*, so that lower dosages (than initially recommended) could be used [15]. It has also a better safety profile than chloroquine (larger therapeutic window). Based on these considerations and some preliminary results from a small clinical study (see below), hydroxychloroquine was preferred over chloroquine as adjunctive treatment since the first release

of this guidance (13<sup>th</sup> of March, 2020), taking also into account that therapy would be likely required mostly in older patients and/or in case of severe disease (at least for the moment). This study, which has meanwhile been published, suggests that SARS-CoV-2 positivity in nasopharyngeal secretions (measured by RT-PCR) is significantly decreased at day 6 after inclusion (i.e. day 10 after symptom onset) in hydroxychloroquine-treated COVID-19 patients (n=26) versus patients who received supportive care only (n=16 external controls). However, several major limitations (small sample size, non-homogeneous compared groups [differences in viral loads, in number of days since onset of symptoms and in quality of follow-up], and rather late HC administration, close to the expected time of viral clearance), make these observations rather weak [16]. In general, the current evidence therefore does not imply a translation of (hydroxy)chloroquine *in vitro* activity to clinically relevant outcomes. Many previous clinical studies of these compounds in other virus infections showed disappointing results. Results of ongoing clinical trials of chloroquine/ hydroxychloroquine efficacy in the treatment of SARS-CoV-2 are eagerly awaited, before STRONG recommendations can be provided for or against the use of these drugs. In the same line, it is not possible at this stage to recommend outpatient use of hydroxychloroquine for patients with mild COVID at risk of complications (risk of toxicity versus uncertain benefit). This could ONLY be considered after a thorough evaluation (see ANNEX 4) in the emergency ward preferentially within a clinical study, and provided the hospital organizes a strict and well organized follow-up and provisions to the patient for the total course of the treatment. Of note, additional stock for plaquenil will be distributed to the hospital pharmacies in the coming days.

Based on pharmacokinetic simulations, the recommended dosing of hydroxychloroquine sulphate is 400mg BID on day 1, followed by 200mg BID on day 2-5. Because of the long elimination half-life of the drug (32–50 days), the duration of treatment should not exceed 5 days to avoid accumulation of hydroxychloroquine concentrations in plasma and tissues, and associated increased risk of toxicity, and because there is no *in vitro* evidence that longer courses improve drug activity on SARS-CoV-2. Considering the precaution concerning G6PD deficiency, we do not recommend a test for G6PD deficiency in all non-European patients. There is no single reported case of acute hemolysis after short courses of (hydroxy)chloroquine. If hospitals consider testing patients, this should not delay the start of the treatment (the test is not widely and immediately available). Because probably patients with G6PD deficiency are aware of their disease, this should be asked at time of admission, and patients specifically followed-up for this adverse event. Cases of hemolysis should be reported through the usual canals (see elsewhere). On a final note, because availability of hydroxychloroquine might become soon problematic, instructions for the use of chloroquine have also been provided in this guidance, but more caution is required.

- **Lopinavir/ritonavir** (400 mg/100 mg BID), initiated more than 12 days post symptom onset (median, IQR [11–17 days]) did not show clinical benefits in hospitalized patients with COVID-19. Moreover, there was no impact on viral excretion. This is in line with *in vitro* experiments with SARS-CoV2 but also SARS-CoV1. In this trial however, a possible benefit (clinical improvement) was suggested in patients who were treated before 12 days of symptom onset, HR 1.25 (0.77,2.05). Lopinavir/ritonavir can still be therefore considered a second choice for the moment, when hydroxychloroquine is contraindicated, but only if this treatment could be administered early in the course of the disease (within 12 days after symptoms onset). We consider this treatment as futile if administered later on.
- **Remdesivir** seems promising *in vitro* (and in some case reports) but availability will remain a key issue for the coming weeks (very restricted use, to the most severe patients, but with also

numerous exclusion criteria [see Table 2], which is unfortunately not the best scenario to test this drug). Several clinical trials are ongoing or planned (Solidarity and DisCoVeRy trials).

- **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.

In accordance with WHO interim guidance [26] and a Correspondence in the Lancet [27], *corticosteroids are not recommended as a systemic adjunctive treatment*. Concerns have also emerged in the social media related to the theoretical interferences between ACE2 receptors (used for viral entry) and some medicines such as angiotensin converting enzyme (ACE) inhibitors /angiotensin receptor blockers (ARBs) as well as non-steroidal anti-inflammatory drugs (NSAIDs). There is so far no scientific evidence of any deleterious effect. 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 (contraindicated in case of renal failure for example). 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. It is important that patients do not interrupt their treatment with ACE inhibitors or ARBs nor be switched to other medicines, but physicians could CONSIDER it in ADMITTED patients if felt necessary. HOWEVER, no changes are advised in suspected/confirmed patients treated at home where no monitoring is possible (the risks outweighing by far the hypothetical benefits).

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://epidemiology.wiv-isp.be/ID/Pages/2019-nCoV\\_procedures.aspx](https://epidemiology.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://epidemiology.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 [28]). 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 [29,30]. **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 [31]. 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) [32,33].** 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) [34]. See additional guidance newborns of COVID-19 positive mothers via the following [link](#) . Antiviral treatment of COVID19 confirmed pregnant women should be considered depending on the safety profile (favorable for (hydroxy)chloroquine or lopinavir/ritonavir, for which large experience exists), maternal risk factors (diabetes, hypertension, asthma) and pregnancy outcome (possible risk of premature delivery in the setting of viral infection) (see also SmPCs in annex 3) [30].

#### **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)* :

FR: [http://gbs-vbs.org/fileadmin/user\\_upload/Unions/PED/Belg\\_Recomm\\_COVID\\_ped\\_31mar\\_FR.pdf](http://gbs-vbs.org/fileadmin/user_upload/Unions/PED/Belg_Recomm_COVID_ped_31mar_FR.pdf)

NL: [http://gbs-vbs.org/fileadmin/user\\_upload/Unions/PED/Belg\\_Recomm\\_COVID\\_ped\\_31mar\\_NL.pdf](http://gbs-vbs.org/fileadmin/user_upload/Unions/PED/Belg_Recomm_COVID_ped_31mar_NL.pdf)

#### **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-Italie) [35]. 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 [36–38]. 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 [35,39,40]. Prophylactic use of LMWH (low molecular weight heparin) in hospitalized cases with COVID-19 is now unanimously accepted, like it would be in any other inpatient with systemic inflammatory/infectious illness. Use of “intensified prophylactic doses” or even “therapeutic doses” of LMWH regimens in individuals at very high risk of thromboembolic events are even suggested by some experts, but the exact dosage, the precise target subgroups of COVID-19 patients and the set of laboratory parameters to support such decision remain undefined at this moment.

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

We therefore currently suggest that:

- In COVID-19 hospitalized patients, oral anticoagulant treatment (prior to admission) is to be replaced by curative LMWH therapy, due to multiple potential drug interactions and difficulties to monitor oral anticoagulation.
- Prophylactic LMWH is indicated in most (if not all) COVID-19 patients who require hospitalization, according to the local institutional protocols, with standard weight adjusted and renal failure dose adjustments.
- Higher LMWH doses (enhanced prophylactic or therapeutic) are to be considered on a careful case by case analysis balancing potential risks and benefits.
- Usual precautions with regards to LMWH safety are of course applicable.

Table 2 : Supportive care & antiviral/immunomodulatory treatment of hospitalized patients with suspected or confirmed COVID-19

Clinical category	Supportive Care	Additional antiviral therapy	Precautions
<b>Suspicion of COVID-19</b> ➤ <b>Mild-to-moderate symptoms (no dyspnea)</b> ➤ <b>No risk group</b> <i>ex. Hospitalization for social-related reasons</i>	Symptomatic treatment	No	Use paracetamol in first-line (usual dosage), and NSAIDs with caution (if really required)
<b>Suspicion of COVID-19</b> ➤ <b>Mild-to-moderate symptoms (no dyspnea)</b> ➤ <b>Risk group<sup>2</sup></b> <b>Or</b> <b>Suspicion of COVID-19 AND alarming symptoms (dyspnea)</b>	<i>Case by case discussion, if possible with an Infectious Disease Specialist, to initiate an empirical antiviral therapy, based on the potential delay to obtain results (antiviral therapy is expected to be more efficient if started early in the course of the disease), or on other considerations (high risk of secondary complications).</i>  <i>If decision to treat empirically (in hospitals), follow the treatment options as described for "CONFIRMED CASES".</i>		
<b>Confirmed COVID-19</b> ➤ <b>Mild-to moderate disease (no O2 requirement/no evidence of pneumonia)</b> ➤ <b>Risk group<sup>2</sup></b>	Symptomatic treatment	<b>Consider start hydroxychloroquine</b> (Plaquenil®) IF NO CONTRA-INDICATION <ul style="list-style-type: none"> <li>• 400 mg at suspicion/diagnosis;</li> <li>• 400 mg 12 h later</li> <li>• Followed by 200 mg BID up to Day 5</li> </ul> <i>NB: when patients improve while on hydroxychloroquine there is no need for delayed hospital discharge, and the 5-day course can be completed at home. The hospital should provide the necessary tablets upon discharge.</i>	<b>Hydroxychloroquine</b>  <b>Contra-indications</b> <ul style="list-style-type: none"> <li>➤ <b>Known allergy to the drug</b></li> </ul> <b>Precautions hydroxychloroquine:</b> <ul style="list-style-type: none"> <li>➤ <b>QTc &gt; 500 msec</b></li> <li>➤ <b>hypokalemia</b></li> <li>➤ <b>drug interaction; check at <a href="http://www.covid19-druginteractions.org">http://www.covid19-druginteractions.org</a> (Liverpool)</b> Interaction potential of hydroxychloroquine is likely the same as chloroquine</li> <li>➤ <b>Known G6PD deficiency</b></li> <li>➤ <b>Myasthenia gravis</b></li> <li>➤ <b>Porphyria</b></li> <li>➤ <b>Retinal pathology</b></li> <li>➤ <b>Epilepsy</b></li> <li>➤ <b>Uncontrolled diabetes</b></li> </ul> <b>NB: pregnancy is not a contra-indication as such</b> (large safety experience with chloroquine); see risk/benefit balance

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

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

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

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

*NB: Sanofi has requested that adverse events related to hydroxychloroquine are reported to [Pharmacovigilance.Belgium@sanofi.com](mailto:Pharmacovigilance.Belgium@sanofi.com)*

*NB: there is no sufficient evidence about activity of azithromycin and therefore no reason to associate this antibiotic to the hydroxychloroquine treatment at this moment*

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

<p><b>Confirmed COVID-19 Severe disease</b></p>	<p>Optimal supportive care in hospital WARD (or ICU)</p>	<p><b>Start hydroxychloroquine</b> (Plaquenil®) IF NO CONTRA-INDICATION</p>	<p>See row above for contraindications and precautions regarding hydroxychloroquine</p>
<p>≥ 1 of the following:</p> <ul style="list-style-type: none"> <li>➤ <b>Respiratory rate</b> ≥30/min (adults); ≥40/min (children &lt; 5)</li> <li>➤ <b>Blood oxygen saturation</b> ≤93%</li> <li>➤ <b>PaO2/FiO2 ratio</b> &lt;300</li> <li>➤ <b>Lung infiltrates</b> &gt;50% of the lung field within 24-48 hours</li> </ul>	<p>Provide O2</p> <p>Administer prophylactic LMWH if not contra-indicated</p>	<ul style="list-style-type: none"> <li>• 400 mg at diagnosis;</li> <li>• 400 mg 12 h later</li> <li>• Followed by 200 mg BID up to Day 5</li> </ul>	<p><i>NB: when patients improve while on hydroxychloroquine there is no need for delayed hospital discharge, and the 5-day course can be completed at home. The hospital should provide the necessary tablets upon discharge.</i></p>
	<p>Consider carefully antibiotics or antifungals</p>	<p><i>NB: If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at</i></p>	

	according to local epidemiology	<p><i>diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 OR chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 500mg BID up to day 5</i></p> <p>Consider <b>lopinavir/ritonavir 400/100 mg</b> (= 2 tablets of 200/50 mg) BID for 14 days) as second choice <b>ONLY</b> if hydroxychloroquine/chloroquine contra-indicated and provided it can be administered within 12 days after symptoms onset (check also drug interaction!); or in children &lt; 10 kg (after IDS advice)</p>	
<b>Confirmed COVID-19 Critical disease</b>	Optimal supportive care in ICU	<b>Remdesivir</b> (compassionate use)	<b>Remdesivir:</b>
<p>≥ 1 of the following:</p> <ul style="list-style-type: none"> <li>➤ <b>Acute Respiratory Distress Syndrome</b></li> <li>➤ <b>Sepsis</b></li> <li>➤ <b>Altered consciousness</b></li> <li>➤ <b>Multi-organ failure</b></li> </ul>	<p>Mechanical ventilation</p> <p>Specific prevention &amp; treatment of ARDS</p> <p>Track secondary bacterial and opportunistic (<i>Aspergillus</i>) infections</p> <p>Prevention of sub-sequent lung fibrosis</p> <p>NB: ongoing studies with dexamethasone, tocilizumab,... in this most critical group</p>	<ul style="list-style-type: none"> <li>• 200 mg loading dose (IV, within 30 min)</li> <li>• 100 mg OD for 2 to 10 days</li> </ul> <p>If remdesivir unavailable: Consider <b>(hydroxy)chloroquine</b>, crushed in nasogastric tube, at the same dosage and monitoring as above; replace with remdesivir if it becomes available</p> <p>However, since the clinical efficacy of (hydroxy)chloroquine is not demonstrated, caution is required in severe cases with kidney/ liver/cardiac failure, and abstention in such situations may be preferred (see above)</p>	<p><b>At this moment very restricted availability of <u>remdesivir</u> (long delay for supply) and very strict criteria released by Gilead</b></p> <p><b>As on 24<sup>th</sup> of March, this drug is restricted in compassionate use for pregnant women and children only.</b></p> <p><b>Request on</b>  <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a>  <b>Inclusion criteria</b>  <b>ICU + confirmation SARS-Cov-2 by PCR + mechanical ventilation</b></p> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>- <b>Evidence of MOF</b></li> <li>- <b>Need of inotropic agents</b></li> <li>- <b>Creatinine clearance &lt; 30 ml/min, dialysis, or hemofiltration</b></li> <li>- <b>Transaminases &gt; 5X ULN</b></li> </ul> <p><b>Of note, remdesivir is one of the treatment arm in the DisCoVeRy trial</b></p> <p>Still limited information on drug interaction is available. Risk-benefit</p>

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*NB: tocilizumab and other interleukins (6 or 1) blockers: Some Chinese, Italian and (very limited) Belgian clinical experience (unpublished) suggest a favorable effect in the most critical patients suffering from persistent and overwhelmed inflammation resembling cytokine release syndrome (CRS). At this moment however, this class of drugs should only be used in clinical trials or within Belgian/international cohort studies if possible. The drug could be considered on an individual basis in patient with persistent inflammation (i.e. elevated IL-6, CRP, D Dimers, ferritin,..) and ARDS requiring mechanical ventilation without evidence of bacterial superinfection/sepsis.*

assessment should be made individually. Close monitoring of remdesivir toxicity or diminished efficacy of concomitant drug is recommended. Check also for interaction with remdesivir at <http://www.covid19-druginteractions> (Liverpool).

## 4. Annexes

### Annex 1: Procedures

#### **Emergency Compassionate use procedure** (as stated in art 107/1 ([link](#)))

At this moment Compassionate use is only available for pregnant women and children <18y old and severe manifestations (see criteria Table 2).

When using Remdesivir for compassionate use (application at Gilead (<https://rdvcu.gilead.com>), a notification to [umn@fagg-afmps.be](mailto:umn@fagg-afmps.be) and to the ethics committee of the concerned site is to be made. The notification should include the following information:

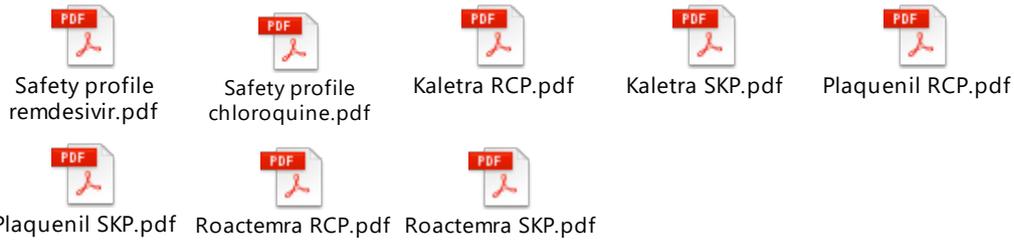
- The name of the sponsor
- The name of the treating physician
- A sworn statement from the physician that the informed consent was obtained in accordance with the law of 22 August 2002 on patient rights
- The indication
- The motivation that without appropriate treatment, it is expected that the patient's 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](mailto: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.notifierunefetindesirable.be](http://www.notifierunefetindesirable.be) or  
[https://www.fagg.be/nl/melden\\_van\\_een\\_bijwerking\\_als\\_gezondheidszorgbeoefenaar](https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar)

## Annex 3: Thorough evaluation for hydroxychloroquine

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



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