INTERIM CLINICAL GUIDANCE FOR PATIENTS SUSPECTED OF/CONFIRMED WITH COVID-19 IN BELGIUM

24 March 2020; Version 5

1. Preliminary note

This document has been revised on the 24th 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 he 24th 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).

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;

(3) the treatment protocols that are in use in some other European countries, as obtained at the beginning of March 2020.

Rows will be added or subtracted to these Tables according to new evidence and recommendations, through regular updates.

IMPORTANT:
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. 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). Participation to multicentric trials will be explored in some hospitals whenever possible but use of standardized case report form during patient management will be strongly encouraged to obtain a fast feedback on any safety issue (in elaboration for remdesivir which is an investigational drug).

Of note, lopinavir/ritonavir and (hydroxy)chloroquine are drugs registered in Belgium for other indications, so that the normal pathway for notification of adverse events has to be used[1]. For compassionate use of 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	*In vitro* activity			*In vivo* activity (animal models)		Clinical studies	Mechanism of action
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	SARS-CoV-1	MERS-CoV		
Remdesivir / GS5734 (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]
Chloroquine phosphate (not marketed in Belgium, but available via import; also available as magistral preparation as	+++ [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];

[1] via www.notifieruneffetindesirable.be or https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar

chloroquine phosphate; 500mg chloroquine phosphate = 300mg chloroquine base); Used for malaria							"immuno-modulation"?
Hydroxy-chloroquine (Plaquenil®); Used for lupus, rheumatoid arthritis	+/-? [14]	Not studied	+++ [15]	Not studied	Not studied	Ongoing for SARS-CoV-2 NCT04261517 Substantial reduction of SARS-CoV-2 respiratory viral load in treated patients compared to placebo [16] Under investigation in the DisCoVeRy trial	Not fully elucidated but assumed to be similar to that of chloroquine
Lopinavir /ritonavir (Kaletra®); Used in HIV infection	+/- [17–19]	- [20]	Not studied	Not studied	+/- [5,21]	Weak efficacy for SARS-CoV-1; associated with ribavirin & cortico-steroids [19] Negative results for SARS-CoV-2 in both a RCT and observational study [22,23]; NCT04252885 Under investigation in the DisCoVeRy trial	SARS-CoV-2 protease inhibition ?

Note : Many other 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, at https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1. At this moment, any of these drug candidates should be evaluated ONLY in clinical trials (see below)

Treatment guidelines used in other countries are indicated in Annex 2.

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 3. The safety profile of chloroquine can be considered as similar to that of hydroxychloroquine.

3. Belgian recommendations for supportive care and adjunctive antiviral treatment for suspected/confirmed COVID-19 cases, according to disease severity.

General guiding principles

Experience with other viral infections tell us that antiviral therapy should be administered as early as possible after symptom onset for optimal effectiveness.

- Chloroquine has good *in vitro* activity against SARS-CoV-2 and seems to reduce the duration of viral shedding. This does not mean that this will be translated in clinical efficacy (many previous experiences were disappointing). Results of ongoing clinical trials are eagerly awaited. This drug 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. 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]. Based on these considerations and some preliminary (pre-published) results from Gautret' study (see below), this option had been preferred in the initial guideline (released on 13th March 2020), taking also into account that therapy will be required mostly in older patients and/or in case of severe disease. Since availability of hydroxychloroquine in sufficient quantity might become a problem, instructions for the chloroquine use will be also provided, but more caution will be required. Results of Gautret' study have been just released and confirm that viral positivity in respiratory secretions (measured by PCR) is significantly decreased at day 6 in hydroxychloroquine-treated COVID-19 patients (n=26) versus those with supportive care (n=16 controls): 30% positivity versus 87.5%, p<0.001). The study has several limitations, acknowledged by the authors, and in particular some differences between the compared groups (no initial randomization). This observation however strongly supports the current choice of hydroxychloroquine as first-line treatment; we suggest to keep the current recommended dosage (see Table), which is pharmacologically very close to that used in Gautret's study (600 mg/day), but do not consider that the proposed 10-day duration of treatment is necessary. Of note, in a small subgroup (n=6) of COVID patients incidentally treated with azithromycin for suspected bacterial superinfection, a more pronounced viral suppression was observed, but this observation is still too preliminary to recommend systematic administration of both drugs concomitantly, taking into account some significant risks of interaction) [16]
- Lopinavir/ritonavir has been recently shown not to provide clinical benefit in hospitalized patients with COVID-19. Importantly, there was also 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 (shorter stay in ICU) was suggested in patient who were treated early (before 12 days of symptoms). 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 10 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).

In accordance with WHO interim guidance [24] and a Correspondence in the Lancet [25], *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, and therefore no robust instruction regarding their use. 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). There is currently no evidence from clinical or epidemiological studies that establishes a link between ACE inhibitors or ARBs and the 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). Any suspected adverse events related to these drugs should be reported through the usual channels, as part of regular pharmacovigilance activities [2].

The table below is aimed to provide some guidance for adjunctive antiviral 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.

It is important for the clinician to be aware that the critical period for complications is 5 to 7 days after symptom onset. Non-hospitalized patients and discharged patients should be advised to re-contact their treating physician in case of clinical deterioration (ex. dyspnea), and reevaluation (ex by daily phone contact) should be considered on case by case evaluation depending on risk factors, social isolation etc.

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 [26]. 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

[2] via www.notifieruneffetindesirable.be or https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar

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 [27,28]. Data on older children are reassuring (no deaths described in children below 10 years old) [29,30]. 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) [31]. 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) [28].

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

Clinical category	Supportive Care	Additional antiviral therapy	Precautions
Suspicion of COVID-19 ➢ **Mild-to-moderate symptoms (no dyspnea)** ➢ **No risk group[3]** ***ex. Hospitalization for social-related reasons***	Symptomatic treatment	No	Use paracetamol in first-line (usual dosage), and NSAIDs with caution (if really required)
Suspicion of COVID-19 ➢ **Mild-to-moderate symptoms (no dyspnea)** ➢ **Risk group[3]** **Or** **Suspicion of COVID-19 AND alarming symptoms (dyspnea)**	*Case by case discussion, if possible with an Infectious Disease Specialist, to initiate an empirical antiviral therapy, based on the potential delay to obtain results (antiviral therapy is expected to be more efficient if started early in the course of the disease), or on other considerations (high risk of secondary complications).* *If decision to treat empirically (in hospitals), follow the treatment options as described for "CONFIRMED CASES".*		
Confirmed COVID-19 ➢ **Mild-to moderate disease (no O2 requirement/no evidence of pneumonia)** ➢ **Risk group[3]**	Symptomatic treatment	Consider start **hydroxychloroquine** (Plaquenil®) IF NO CONTRA-INDICATION • 400 mg at suspicion/diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up to Day 5 *NB:*	**Contra-indications hydroxychloroquine** ➢ **Known allergy to the drug** **Precautions hydroxychloroquine:** ➢ **QTc > 500 msec** ➢ **drug interaction; check at** http://www.covid19-druginteractions.org **(Liverpool)** Interaction potential of hydroxychloroquine is likely the same as chloroquine

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

		stop hydroxychloroquine if follow-up at home *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.*	➢ **Myasthenia gravis** ➢ **Porphyria** ➢ **Retinal pathology** ➢ **Epilepsy** **NB: pregnancy is not a contra-indication as such** (large safety experience with chloroquine); see risk/benefit balance Perform ECG daily if initial QTc 450-500 msec, and biochemistry according to underlying disease *NB: Sanofi has requested that adverse events related to hydroxychloroquine are reported to* Pharmacovigilance.Belgium@sanofi.com
Confirmed COVID-19 Severe disease **≥ 1 of the following:** ➢ **Respiratory rate ≥30/min (adults); ≥40/min (children < 5)** ➢ **Blood oxygen saturation ≤93%** ➢ **PaO2/FiO2 ratio <300** ➢ **Lung infiltrates >50% of the lung field within 24-48 hours**	Optimal supportive care in hospital WARD (or ICU) Provide 02 Consider carefully antibiotics or antifungals according to local epidemiology	Start **hydroxychloroquine** (Plaquenil®) IF NO CONTRA-INDICATION • 400 mg at diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up to Day 5 *NB: If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 OR chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 500mg BID up to day 5* Consider **lopinavir/ritonavir 400/100 mg** (= 2 tablets of 200/50 mg) BID for 14 days) *as second choice ONLY if hydroxychloroquine/chloroquine contra-indicated and provided it can be administered within 10 days after symptoms onset (check also drug interaction!); or in children < 10 kg (after IDS advice)*	**Contra-indications hydroxychloroquine:** ➢ **Known allergy to the drug** **Precautions hydroxychloroquine:** ➢ **QTc > 500 msec** ➢ **drug interaction (check at** http://www.covid19-druginteractions.org **(Liverpool)** Interaction potential of hydroxychloroquine is likely the same as chloroquine ➢ **Myasthenia gravis** ➢ **Porphyria** ➢ **Retinal pathology** ➢ **Epilepsy** **NB: pregnancy is not a contra-indication as such** (large safety experience with chloroquine); see risk/benefit balance **NB: use with caution if renal impairment, taking into account the paucity of PK data**; keep the same loading dose (D1) but decrease the D2-D5 dose to 50% if GFR between 10 and 30 ml/min, and to 25% if GFR < 10 ml/min or dialysis (very weak evidence) Perform basic biochemistry daily and ECG daily if initial QTc > 450 msec (+ other indicated investigations)

			Avoid quinolones if possible, or monitor closely the QT if these antibiotics are needed *NB: we stress again that there is no sufficient evidence about activity of azithromycin and therefore no reason to associate this antibiotic to the hydroxychloroquine treatment at this moment*
Confirmed COVID-19 Critical disease **≥ 1 of the following:** ➢ **Acute Respiratory Distress Syndrome** ➢ **Sepsis** ➢ **Altered consciousness** ➢ **Multi-organ failure**	Optimal supportive care in ICU Mechanical ventilation Specific prevention & treatment of ARDS Track secondary bacterial and opportunistic (*Aspergillus*) infections Prevention of sub-sequent lung fibrosis NB: ongoing studies with dexa-methasone, tocilizumab,… in this most critical group	**Remdesivir** (compassionate use) • 200 mg loading dose (IV, within 30 min) • 100 mg OD for 2 to 10 days If remdesivir unavailable: Consider **(hydroxy)chloroquine,** crushed in nasogastric tube, at the same dosage and monitoring as above; replace with remdesivir if it becomes available 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) *NB: tocilizumab and other interleukins (6 or 1) blockers: Some preliminary Chinese and Italian data and very limited clinical experience in Belgium 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*	**At this moment very restricted availability of remdesivir (long delay for supply) and very strict criteria released by Gilead** **As on 24th of March, this drug is restricted in compassionate use for pregnant women and children only** **Request on** https://rdvcu.gilead.com/ **Inclusion criteria** **ICU + confirmation SARS-Cov-2 by PCR + mechanical ventilation** **Exclusion criteria** - **Evidence of MOF** - **Need of inotropic agents** - **Creatinine clearance < 30 ml/min, dialysis, or hemofiltration** - **Transaminases > 5X ULN** **Of note, remdesivir is one of the treatment arm in the DisCoVeRy trial** 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 (Liverpool).

	clinical trials or within 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,..) without evidence of bacterial superinfection/sepsis and ARDS requiring mechanical ventilation.

4. Annexes

Annex 1: Procedures

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

When using Remdesivir for compassionate use (application at Gilead (https://rdvcu.gilead.com), 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.

Annex 2: Therapies for confirmed COVID-19 in some European countries

Disease category	Italy (Lombardia protocol)	France	Netherlands	Switzerland
➢ **Mild-to-moderate disease** ➢ **No risk group**	No antiviral treatment	No antiviral treatment	No antiviral treatment	No antiviral treatment
➢ **Mild-to-moderate disease** ➢ **Risk group**	lopinavir/ritonavir + chloroquine or hydroxychloroquine for 5-7 days	Consider lopinavir/ritona-vir; duration depending on monitoring of viral excretion	Consider chloroquine for 5 days	? (not mentioned)
➢ **Severe disease**	remdesivir + chloroquine or hydroxychloroquine for 5-20 days (if no remdesivir: maintain lopinavir/ritonavir with chloroquine)	remdesivir; duration depending on monitoring of viral excretion (No second choice)	chloroquine D1 (600-300 mg; D2-D5 300 mg BID) lopinavir/ritona vir as second option (for 10-14 days)	Lopinavir/ritonavir (atazanavir/ritonavir as second choice)
➢ **Critical disease**	remdesivir + chloroquine or hydroxychloroquine for 5-20 days (if no remdesivir: maintain lopinavir/ritonavir with chloroquine)	remdesivir; duration depending on monitoring of viral excretion Lopinavir/ritona vir as second choice (case by case)	remdesivir (for 10 days) + chloroquine (for 5 days)	remdesivir as first choice (for 10 days) lopinavir/ritonavir (+ hydroxychloroquine if < 65 years/no comorbidity) as second choice (if remdesivir unavailable). Tocilizumab (in case of MOF and inotropic support)

Annex 3: Safety profiles

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

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