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

June 2021; Version 20

Preliminary note

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.

This document is periodically revised 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 COVID-19 cases during the epidemic in Belgium. This guideline primarily targets hospital care but refers whenever necessary to other guidelines.

The guidance has been developed from March to December 2020 by a task force of Infectious Diseases Specialists (IDS): Dr Sabrina Van Ierssel, Universitair Ziekenhuis Antwerpen; Dr Nicolas Dauby, Hôpital Universitaire Saint-Pierre Bruxelles; Dr Emmanuel Bottieau, Instituut voor Tropische Geneeskunde (ITG), and Dr Ralph Huits, ITG, supported by Sciensano (Dr Chloe Wyndham-Thomas;), the AFMPS/FAGG (Dr Roel Van Loock) and ad-hoc contributions from colleagues of other disciplines. Since January 2021, the COVID-19 therapeutic guideline has officially been taken over by the Belgian Society of Infectiology and Clinical Microbiology (BVIKM/SBIMC), and the new task force is composed of IDS representatives from all Belgian University Hospitals, with the additional collaboration of the Belgian Societies of Intensive Care Medicine and of Pneumology. The complete list of members is available below, and the conflicts of interest statements of all participants is available upon request at BVIKM/SBIMC (elise.brisart@sbimc-bvikm.be).

This guidance is based on the best clinical evidence (peer-reviewed scientific publications) that is available at the moment of writing each update, and is purposed to be a "living guideline" which can always be found via the same link. Keeping the guidelines 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 publications, including from the grey literature, and contribution in priority to Dr Maya Hites (maya.hites@erasme.ulb.ac.be) and Dr Emmanuel Bottieau (ebottieau@itg.be). We take this opportunity to thank again the countless readers who, since this guideline was initially released, flagged the inconsistencies, typos or unclear text, as well as those who sent all types of contributions related to this rapidly evolving field.

Of note, this document will not describe in detail the generic and supportive management of COVID-19 (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); the strengths of the recommendations are now provided using the GRADE score [2].
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, clinical evidence for treatment with monoclonal antibodies (Table 2) and *in vitro/in vivo* efficacy of select antiviral drugs (Table 3).
4. An overview of the ongoing clinical trials in Belgium (Table 4).
5. Annexes, covering compassionate use and import procedures.
6. References

IMPORTANT

As a rule, only manuscripts ACCEPTED after a rigorous PEER-REVIEW process will be used for the strong recommendations in this guidance. 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.

This document will not describe in detail the generic and supportive management of COVID-19 (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 preclinical pipeline.

Use of off label or investigational antiviral or immunomodulatory drugs should be reserved to clinical studies/trials only and efforts are undertaken by the KCE to support non-commercial multicentric studies in Belgium. In addition, use of standardized case report forms is strongly encouraged during patient management, in order to obtain a fast feedback on safety issues and patient outcomes.

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A conflict of interest list for the members is available here

1. Executive summary

Table 1 : Supportive care & antiviral/immunomodulatory treatment of hospitalized adult patients with suspected or confirmed COVID-19 infection

Clinical category	Supportive Care	Additional therapy (Strength of recommendation - GRADE)
Suspicion of COVID-19 ➢ **Mild-to-moderate symptoms (no dyspnea)** ➢ **No risk group** *ex. Hospitalization for social reasons*	Symptomatic treatment	No (Strong recommendation, low-quality or very low quality evidence - 1C)
Suspicion or confirmed COVID-19 ➢ **Mild-to-moderate symptoms (no dyspnea)** ➢ **Risk group**[1]	Symptomatic treatment	Insufficient data at this moment to recommend for or against any drug in routine in mild to moderate disease. Use preferentially in clinical trials (Strong recommendation, low-quality or very low quality evidence - 1C) Consider **monoclonal antibodies** on a case-by-case basis after balancing individual risks and benefits, provided these therapeutics are administered early after infection onset (no supplemental oxygen requirement) in a hospital setting among patients at high risk for clinical deterioration (weak recommendation, low-quality of evidence; based on demonstrated antiviral effect, but not hard clinical outcome data).
Confirmed COVID-19 Severe disease **≥ 1 of the following:** ➢ **Respiratory rate ≥30/min (adults); ≥40/min (children < 5y)** ➢ **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 O_2 Administer prophylactic LMWH if not contra-indicated Consider carefully antibiotics or antifungals according to local epidemiology	**Dexamethasone** 6 mg once a day for up to 10 days (or until hospital discharge if sooner), IV or PO; (Strong recommendation, high-quality evidence - 1A). If dexamethasone is not available, equivalent doses of corticosteroids can be used (hydrocortisone 150 mg/d or methylprednisolone 32 mg/d or prednisone 40 mg/d) (Strong recommendation, moderate quality of evidence - 1B). Case by case decision for children and pregnant women pending additional results and with the respective specialists. **Combination of dexamethasone and remdesivir** has not been studied in randomized clinical trials, but can be considered, based on an individual risk/benefit analysis* in rapidly progressing COVID-19. **Remdesivir** should preferentially be given to patients <5 days of symptom onset (Weak recommendation for combination therapy dexamethasone + remdesivir, moderate quality of evidence - 2B). • 200 mg loading dose (IV, within 30 min) • 100 mg once daily for day 2 to day 10**

[1] Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,…), diabetes, coronary artery disease, chronic obstructive pulmonary disease, arterial hypertension, obesity (BMI>30), immunosuppressed
LMWH: low molecular weight heparin

		Tocilizumab and other interleukin 6 blockers: consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (Conditional recommendation, low quality of evidence)

**Note that recent data suggests potential kidney toxicity, to take into account in the individual decision. As with all adverse events, occurrence of renal toxicity with remdesivir should be reported to AFMPS/FAGG.*

*** A minimal 5-day treatment course should be given, with a possibility of a one-off extension of 5d if unsatisfactory clinical response. Given the limited availability of remdesivir the treatment should not be given longer than necessary (cfr annex 1 for details on remdesivir availability)*

Clinical category	Supportive Care	Additional therapy (Strength of recommendation - GRADE)
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 Administer prophylactic LMWH if not contra-indicated Specific prevention & treatment of ARDS Track secondary bacterial and opportunistic (*Aspergillus*) infections Prevention of sub-sequent lung fibrosis	**Dexamethasone** 6 mg IV (or equivalent doses of corticosteroids, see row above) once a day for up 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists (Strong recommendation, high-quality evidence - 1A). Consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19, (Conditional recommendation, low quality of evidence)

ARDS: Acute respiratory distress syndrome. LMWH: low molecular w eight heparin

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: Pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. In patients with eGFR < 30mL/min, the benefits & risks are to be weighed [3]
  - Possible bradycardia: Post-marketing study based on the World Health Organization pharmacovigilance database identified increased reports of serious bradycardia among patients treated with remdesivir. Remdesivir was the sole suspected drug among 93% of patients (n=88) [4]
- 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 (Liverpool).
- More information on warnings/precautions of use in Veklury product information .
- Registered for treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg). For pregnant women & children: compassionate use is possible, request on 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 (or if not available equivalent doses of corticosteroids) be considered as a standard of care in severe and critical COVID-19 disease (grade 1A). Background data and rationale behind these recommendations are detailed here. Latest results concerning additional antiviral and immunomodulatory treatments are also covered hereunder.

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

2.1. Corticosteroids

2.1.1. Dexamethasone, systemic corticosteroids

In accordance with World Health Organization (WHO) interim guidance [5] and a Correspondence in the Lancet [6], 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 UK-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) [7]. 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 (12.3 by chi-square test for trend). 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) [8], CoDEX (Brazil) [9], and CAPE COVID (France) [10]. 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 [11]. The conclusion was robust throughout all trials (n=678 in total versus 1025 in placebo/usual care arm, all critically ill patients): administration of 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 exact details concerning the implementation in clinical practice is lacking, the consistent findings

of benefit provide definitive data that corticosteroids should be first-line treatment for critically ill patients with COVID-19 [12]. In case dexamethasone is not available, WHO recommends using equivalent doses of other corticosteroids (see Table 1; executive summary) [11].

Notes on treatment with systemic corticosteroids:

It is currently unknown whether the use of corticosteroids in COVID-19 is independently associated with an increased risk for bacterial or fungal infection. A systematic review with meta-analysis complemented the 7 RCTs analyzed in [11] with 37 retrospective observational studies, covering 20.197 patients [13]. Diverse corticosteroid regimens were investigated, most of which consisted of methylprednisolone; 16/29 and 11/29 studies used respectively high (>1mg/kg prednisolone) and lower (<1mg/kg prednisolone) doses. A trend towards more antibiotic use and more infections (6 studies) was noted; however overall pooled estimate showed a reduced mortality in the corticosteroid-treated patients (OR 0.72; 0.57-87), which is in a range similar to that found in the WHO REACT working group meta-analysis [11].

The risk versus benefit of late corticosteroid therapy in patients with COVID-19 associated ARDS is currently not known. A post-hoc analysis of a multicenter dataset of 348 patients with moderate to severe ARDS associated with COVID-19 admitted to 21 French and Belgian ICUs, comparing with and without corticosteroid-treatment after 13 days of symptom onset did not find a difference in ICU mortality (HR 1.44; 0.83-2.50) or duration of mechanical ventilation (HR 0.89; 0.60-133) [14]. No studies have addressed the question whether a prolonged course or a second course of corticosteroids influence the outcome in COVID-19 patients who remain ventilator dependent following a standard course of corticosteroids as provided in the RCTs. A systematic review and trial sequential meta-analysis was performed analysing the use of corticosteroids in patients with ARDS due to COVID-19 and non-COVID-19 related etiology. The use of corticosteroids was found to probably reduce 28-d mortality (RR 0.82; 0.72-0.95) regardless of etiology, and to probably reduce the duration of mechanical ventilation (mean difference 4d fewer, 2.5-5.5), but the optimal information size was not reached in the trial sequential analysis. Among the pooled analysis of COVID-19 and non-COVID-19 patients, those who received >7d of corticosteroids had lower mortality than those who received a ≤7d course (p=0.04) [15].

Effect of low-dose and short-course corticosteroids on risk of *Strongyloides* reactivation is not well known. Nevertheless, for high-risk patients, such as originating from *Strongyloides* endemic areas, empirical ivermectin treatment should be considered before, or early during, corticosteroid administration treatment [16].

2.1.2. Inhaled corticosteroids

The possible benefit of inhaled corticosteroids in early COVID-19 (<7 days after symptom onset) was investigated in a phase-II open label RCT in the UK [17]. The trial was stopped early because of a reduced number of new cases. Independent statistical review concluded that the study outcome would not change with further participant enrolment. The patients in the budesonide group had a significantly lower probability of an urgent care visit (15% vs 3%). Number needed to treat to avoid an urgent care visit was eight. Self-reported clinical recovery was shortened by 1 day (median 7 days [95% CI 6–9] vs 8 days [7–11]; log-rank test p=0.007). This is the first published trial with inhaled corticosteroids in COVID-19. Several similar trials are still ongoing.

Preliminary data from two other RCTs on inhaled corticosteroids in COVID-19 are available. The PRINCIPLE trial investigated 2x800µg inhaled budesonide added to standard care in (suspected) COVID-19 patients in the community, aged ≥65y or ≥50y with co-morbidities and ≤14d symptoms and found a shorter time to recovery (minus 3d; CI: 1-5.4) without an effect on hospitalization rate in the budesonide arm [18].

Results of a phase-III RCT placebo controlled trial on inhaled ciclesonide, including 400 non-hospitalized patients with symptomatic COVID-19 were announced as a press release: no significant differences were found in time to alleviation of COVID-19 related symptoms (primary endpoint) although a reduction in the number of hospitalizations or emergency department visits was observed in one of the secondary endpoints (link). In an advice dated 27/5/2021, EMA considered the evidence published thus far as insufficient to recommend the use of inhaled corticosteroids in COVID-19, as the possibility of harm in patients not requiring additional oxygen as yet cannot be excluded (link).

2.2. Remdesivir

Main message: The WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of the severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.

Remdesivir (RDV) seemed promising *in vitro* and in non-human primates models [19]. 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 [20]. In this study (where median delay from symptom onset to enrolment was quite long, 11 days in the RDV group), 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 final report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US has been published [21] confirming a faster recovery in remdesivir-treated hospitalized COVID-19 patients with evidence of pneumonia (n=541) compared to patients given placebo (10 days instead of 15 days; recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p<0.001). The benefit was most apparent in those COVID-19 patients receiving low-flow oxygen, the largest group of patients included in the study, and when remdesivir was given before the 10th day of symptom onset. Results were not conclusive for other groups of patients (those not requiring supplemental oxygen, or in patients requiring mechanical ventilation). No statistical difference was seen for mortality by Day 15 (6.7% mortality versus 11.9%) and by Day 29 (11.4 versus 15.2%), but there was a positive trend compared to placebo (hazard ratio: 0.73 95% CI 0.52 to 1.03).

In addition, a randomized, open-label, phase 3 trial, comparing 5-day and 10-day treatment with remdesivir in patients with severe/critical disease (oxygen requirement), 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 [22].

A third RCT sponsored by Gilead (Spinner et al.) assessed the role of RDV in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) [23]. 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 [20]. In a study performed in the rhesus macaque, initiation of RDV very early after infection (12 hours) obtained better clinical outcome and reduced lung viral replication [19]. This suggests that the impact of RDV would only be expected very early on in the infection.

On 3 July 2020, following European Medical Agency (EMA) evaluation, the European Commission 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 (for dosage and precautions see Table 2).

The effect of remdesivir may appear as clinically modest but a reduction of hospital stay could be very useful when resources are overstretched. All in all however, the precise indication remains uncertain because the optimal patient population, the optimal treatment duration and the actual impact on outcome are still unclear [24].

In December, the results of the SOLIDARITY multicenter worldwide pragmatic trial were published, showing no overall clinical benefit of remdesivir in hospitalized patients with COVID-19. Remdesivir was evaluated in 2743 patients, compared to 2708 controls. In a meta-analysis of the 4 published trials on remdesivir, a weighted average of the results from all trials yielded a rate ratio for death (remdesivir vs. control) of 0.91 (95% CI, 0.79 to 1.05). However, in the subgroup of patients receiving no mechanical ventilation at time of randomization, the rate ratio for death was 0.80 (0.63-1.01) [25]. The WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of the severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. Nevertheless, WHO continues to endorse including patients in trials with remdesivir to establish with certainty whether remdesivir has a positive effect on survival in mild to moderate, hospitalized COVID-19 patients. The Solidarity and Discovery trials continued to randomize mild to moderate hospitalized COVID-19 patients to receive remdesivir vs. standard of care. However, the Solidarity Trial announced on the 27th of January, and the Discovery trial on the 29th of January that inclusions into the remdesivir arm have been stopped due to futility in severe, but also mild to moderate, hospitalized COVID-19 patients.

In addition, EMA evaluated the full mortality and viral data from NIAID ACTT-1 data upon which EMA recommended to not start remdesivir in COVID-19 patients already on mechanical ventilation and on ECMO. This guidance, that already considers remdesivir as having a modest effect and small window of use, will be further updated when the data from the Discovery and Solidarity trials are published. A recent meta-analysis of the 5 published RCTs on remdesivir vs. control has also shown the modest effect of remdesivir in hospitalized patients. Patients in the remdesivir treatment group had a greater likelihood of hospital discharge, and clinical improvement was more rapid than the control group, yet no effect was observed on mortality [26].

Finally, as dexamethasone is now considered the standard of care for hospitalized patients requiring oxygen or on mechanical ventilation, it is important to highlight that there is almost no data on the impact of

combining dexamethasone and remdesivir on outcome. Nevertheless, a retrospective analysis of a cohort of 2315 patients hospitalized for COVID-19 in the USA, among whom 342 patients received remdesivir (184 who also received corticosteroid treatment), failed to show a reduced risk of death at 28 days in the remdesivir and corticosteroids arm compared to remdesivir alone [27].

2.3. Immunomodulatory agents, anti-interleukin therapy

Immunomodulatory agents are a varied group of drugs that may prevent or dampen hyper-inflammatory responses which are associated with clinical deterioration and mortality [74,75]. Several interleukin (IL) and complement blockers used in inflammatory diseases such as giant cell vasculitis or rheumatoid arthritis have been proposed for repurposing based on limited clinical experience and small observational studies. These drugs include tocilizumab (IL-6-receptor antagonist) [76,77], sarilumab (IL-6 receptor antagonist), siltuximab (anti-IL-6) and anakinra (IL-1-receptor antagonist), as well as complement inhibitors such as C3 and C5 inhibitors, C5a receptor inhibitors and C1 esterase inhibitors. Eight randomized trials assessing the use of tocilizumab (TCZ) in hospitalized COVID-19 patients have been recently published [78–80]. These trials were highly heterogeneous regarding the severity of the patients included.

In their most recent guidelines, the Infectious Diseases Society of America (IDSA) has formulated a conditional recommendation with low certainty of evidence, towards the addition of tocilizumab to standard of care (i.e. steroids) rather than standard of care alone, in hospitalized adults with progressive severe ($SpO2 \leq 94\%$ on room air, including patients on supplemental oxygen) or critical (mechanic ventilation and ECMO) COVID-19 who have elevated markers of systemic inflammation [81]. In the largest trial on treatment with tocilizumab, the criterion for systemic inflammation was defined as CRP >75 mg/L. Both RECOVERY and REMAP CAP (the two tocilizumab trials that reported a benefit) initiated treatment early (randomization at median of two days of hospitalization in RECOVERY; <24 hours in the ICU for REMAP-CAP), suggesting tocilizumab may be more beneficial in people with early rapidly progressive disease.

Notes on treatment with immunomodulatory agents:

Caution must be exercised when used in patients with active concomitant (myco-) bacterial and fungal infections and in chronically immunosuppressed patients. Alternative inflammatory markers instead of CRP (such as procalcitonin) could be used for monitoring of surinfection in patients treated with IL-6-blockers.

These drugs are intensively investigated including in Belgium (see Table 3). Notably, the multicentre COV-AID trial has completed enrollment and should provide answers soon regarding the impact of IL-6 blockade and combined IL-6/IL-1 blockade in our Belgian setting. Of note, inclusion was based on a combination of biological factors (to better select suitable candidates), in contrast with other trials. Recently, clinical trials using Anakinra were temporarily suspended in France; but recruitment is permitted again. Of note, the French trials used higher dosages as compared to those used in Belgium and the DSMB of the COV-AID trial has considered that Anakinra could be further evaluated in Belgium. There is no RCT evidence yet for recommending their use outside studies. Potential adverse events and drug interactions have to be carefully taken into consideration.

2.4. Monoclonal antibodies

Dozens of monoclonal antibodies (mAbs) targeting the Receptor Binding Domain (RBD) of the spike protein (S protein) have been developed [88] and more than 50 trials are being conducted. Given the long half-life, a single injection (mostly intravenous, subcutaneous and intramuscular routes are under study) is generally used and could prevent disease progression or infection [89]. On the 26th of February 2021, the EMA's human medicine committee (CHMP) concluded that casirivimab and imdevimab could be used together to treat COVID-19 patients not requiring supplemental oxygen and at high risk of complication. The same decision was made for bamlanivimab and etesevimab (5th of March), regdanvimab (26th of March) and for sotrovimab (21th of May). On 19 May 2021, a Ministerial Decision allow conditional use of REGN-COV2, published in the Moniteur belge/Belgisch staatsblad (link).

Due to the broad spectrum of available monoclonal antibodies and heterogeneity in combined treatment regimens, this section is split according to the available evidence per molecule and combinations thereof. A summary table with an overview is provided in chapter 3 (Table 2).

Bamlanivimab + etesevimab, casirivimab + imdevimab, regdanvimab or sotrovimab can be considered for treatment on a case-by-case basis among COVID-19 patients with mild to moderate disease severity. Namely, these therapeutics have to be administered early after infection onset (no oxygen requirement) among patients at high risk for clinical deterioration. It is important to stress that very early administration might be extremely challenging in the current situation because it necessitates appropriate hospital infrastructure and excellent collaboration with primary care. These mAbs have not been specifically studied in immunosuppressed patients, a group for which such treatment seems attractive. Furthermore, efficacy studies against new emerging SARS-CoV2 variants are necessary. Viral monitoring during mAbs therapy is suggested to monitor the risk of developing resistance during treatment. SARS-CoV-2 variant classifications and definitions are available via the CDC (link). Treatment with monoclonal antibodies can be considered on a case-by-case basis, after balancing individual risks and benefits, provided these therapeutics are administered early after infection onset (no oxygen requirement) among patients at high risk for clinical deterioration.

2.4.1. Bamlanivimab

A phase II RCT with bamlanivimab (BLAZE-1, NCT04427501) in mild and moderate COVID-19 outpatients showed promising results on viral decline, symptom resolution and hospitalization [97]. For hospitalized patients with more advanced disease (trial conducted by the ACTIV-3/TICO LY-CoV555 Study Group), bamlanivimab (co-administered with remdesivir) did not demonstrate any clinical benefit [98]. In a US real-world experience case-control study of 403 high-risk outpatients (including 27% immunosuppressed patients) with mild or moderate COVID-19, fewer number of hospitalizations on day 30 were observed in the group treated with bamlanivimab infusion. However, the reasons for non-administration of bamlanivimab for the majority of patients in the control group are not recorded. No adverse events requiring hospitalization were reported in that study [94].

2.4.2. Bamlanivimab + etesevimab

The phase 2/3 portion of BLAZE-1 outpatients treated with the combination of bamlanivimab and etesevimab, administered together in a single infusion, showed a significant reduction in viral load on day 11, while no significant change was seen on viral load with bamlanivimab alone. Among secondary endpoints, there were no consistent differences between the monotherapy and the combination therapy versus placebo for the other measures of viral load or clinical symptom scores [99]. In the unpublished RCT, phase 3, BLAZE-1 trial,

including outpatients with mild or moderate COVID-19, at high risk for progressing to severe COVID-19 who received an intravenous infusion of 2800 mg bamlanivimab + 2800mg etesevimab, a 70% reduction of hospitalization and death by any cause by day 29 was observed [100]. These data are to be confirmed by a publication. According to the unpublished results of the BLAZE-4 phase 2 trial, the only authorized dose of bamlanivimab is 700 mg combined with etesevimab 1400 mg (link).

2.4.3. Casirivimab + imdevimab

In an interim analysis of a phase 2-3 trial studying the effect of a combination regimen of casirivimab and imdevimab (NCT04425629) on 275 outpatients, a significant decline in viral load on day 7 was observed when compared to placebo, especially in seronegative patients and in patients with high viral load [101]. However, the impact on clinical outcomes (medically attended visit) were less clear. A preprint article elaborated further on the results of the phase 3 portion of this same study in high-risk outpatients who received various doses of REGEN-COV (2400mg vs 1200mg vs placebo). The results showed that both REGEN-COV dosage regimens significantly reduced hospitalization or death by day 29 (respectively 71.3% reduction [1.3% vs 4.6%] and 70.4% [1.0% vs 3.2%]) [102]. Efficacy of REGEN-COV was consistent across subgroups, including patients that were SARS-CoV-2 seropositive at baseline. Results of a phase 3 trial on subcutaneous REGEN-COV prophylaxis among household contacts exposed to SARS-CoV-2 at home (NCT04452318) showing a 72% protection against symptomatic infections within the first week have been communicated via press release.

2.4.4. Regdanvimab

A phase 2-3 trial of 325 adult outpatients with COVID-19 (study CT-P59, unpublished) showed a lower proportion of severe COVID-19 (hospitalization, oxygen requirement or death) by day 28 of 4.4% when analysing pooled dosage regimens of CT-P59 (40mg/kg and 80mg/kg) versus 8.7% in the placebo group (link).

2.4.5. Sotrovimab

The interim results analysis of the unpublished phase 3 COMET-ICE trial (NCT04545060), evaluating a single 500 mg infusion of sotrovimab compared to placebo in 868 high-risk outpatients (most common risks factors: obesity: 63%, >55 years: 47% and diabetes: 23%) demonstrated an 85% (p=0.002) reduction in hospitalization or death at day 29 in the sotrovimab group (link). In addition, results from in-vitro and animal model in a pre-print study seem to demonstrate that VIR-7831 maintains activity against currently circulating variants of concern, including the India variant (B.1.617) [103].

2.5. Convalescent plasma

Animal studies with SARS-CoV-1 and SARS-CoV-2 infections indicate a protective role of neutralizing antibodies. In addition to marked antiviral activity, plasma administration has been associated with decreased inflammatory markers in a trial in India [82]. Several observational studies, non-controlled and controlled non-randomized trials, and four RCT's have been published [83]. Observational studies show survival benefit of transfusing COVID-19 convalescent plasma (CCP) with high antibody titers [84]. In contrast, 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) [85].

An Indian multicenter open label RCT in severe non critically ill COVID-19 patients (P/F 200-300mmHg or RR>24 + SatO2 ≤ 93% with FiO2 21%) did not show any reduction in disease progression and all-cause mortality at D28 (19% vs 18%). However, an antiviral effect was demonstrated as well as a faster resolution of dyspnea. In this study post-hoc analysis showed low levels of neutralizing antibodies in the administered plasma and detected neutralizing antibodies in 79% of patients at baseline [86] . This concurs with the Dutch RCT that was stopped early due to the finding of comparable amounts of neutralizing antibodies in patients as in the administered convalescent plasma, as early as median 10 days after symptom onset [87]. A large placebo-controlled randomized trial from Argentina did not find an impact on mortality of administration of CP containing high titers of neutralizing antibodies. However, 29% of the patients in the plasma arm were critically ill [88]. The RECOVERY trial randomized 11,558 patients to convalescent plasma or usual care. They did not find any difference in 28d mortality between the two groups (both 24%). There was also no difference in secondary outcomes such as discharge at day 28 or progression to mechanical ventilation or death in those not mechanically ventilated at randomization [89]. A Cochrane review including some republished data including those of the RECOVERY trial, and a meta-analysis performed by the RECOVERY group, did not find a difference in mortality [89,90]. The REMAP-CAP study also halted recruitment in de convalescent arm due to futility. Until now the data have not yet been published.

An Argentinian blinded RCT evaluated early (i.e. within 3d of symptom onset) administration of convalescent plasma in older COVID-19 patients, i.e. >75y or >64 -75y with comorbidities [91]. They found a RR reduction of 0,52 (95% CI 0,29-0,94). The study was terminated early due to a fall in the COVID-19 incidence in Argentina, including 76% percent of the provided inclusion number. On the other hand, the NIH trial C3PO evaluating convalescent plasma for treatment of early-onset (<7 days) non-hospitalized COVID-19 patients was halted as interim analysis of 511 participants (of the 900 planned) found no clinical benefit (link).

Notes on treatment with convalescent plasma:

We only recommend the administration of convalescent plasma within clinical trials in Belgium such as the CONFIDENT study that is currently ongoing (of note recruitment is closed for the DAWN-plasma trial). At this moment there are no clinical trials in Belgium on early administration of COVID-19 convalescent plasma (CCP) in risk groups. 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 RKV/CR center. AFMPS/FAGG has recommended that donation should only take place more than 28 days after symptoms have ended. Of note, administration of CCP could be considered in case of persistent viral shedding (> 1 month) in severe COVID-19 patients with B cell-related immunosuppression (including patients on Rituximab and other B-cell depleting agents) unable to mount an antibody response, as shown in a French case series by Heuso et al [92] and other case series. The volume and antibody titer used in different reports varies [93].

A MEURI (Monitored Emergency Use of Unregistered Investigational Interventions) protocol, similar to the Urgent Medical Need program of the FAGG/AFMPS/AFMHP was established by RKV/CR to obtain CCP for these very restricted situations where inclusion in the current clinical trials (CONFIDENT-plasma) is not possible. CCP is a standard fresh frozen plasma from convalescent voluntary donors with SARS-CoV-2 neutralizing antibodies and conforms to all legal criteria. Criteria for this MEURI delivery, including the requirement for registration of clinical data, are defined and available via your hospital's blood bank laboratory or RKV/CR. Of note, emergence of viral populations with significant mutations in the spike protein has been reported during treatment of immunocompromised patients with convalescent plasma

[94]. Furthermore, the genomic differences between SARS-CoV-2 variants globally and regionally affect response to convalescent plasma treatment. Formal studies evaluating the value of convalescent plasma in this setting are needed [95,96].

2.6. Janus kinase inhibitors

2.6.1. Baricitinib

Baricitinib is an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2. In a randomized placebo-controlled trial in patients with moderate and severe COVID-19, treatment with baricitinib 4mg qd and remdesivir was shown to reduce recovery time and to accelerate improvement in clinical status when compared to remdesivir alone [28]. Corticosteroids were not considered standard of care in this study. It's currently unclear whether the benefit of baricitinib with remdesivir would reach the benefit of steroids alone. Prices of baricitinib and remdesivir are significantly higher than steroids, so this treatment should not be used as a standard pending further evaluation, including use without remdesivir, use on top of steroids or use in comparison with steroids. One large double blind randomized placebo-controlled trial (SOC included systemic corticosteroids in 80% of patients) showed no influence of baricitinib on combined primary endpoints (progression to requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death by day 28), but there was a significant reduction of mortality at day 28 and day 60 [29]. Baricitinib, according to a press release (link) on 2 February 2021, is to be investigated as a possible treatment for COVID-19 in the RECOVERY trial. On the 29th of April, the EMA has begun the evaluation of an application to extend the use of Olumiant (baricitinib) to include treatment of COVID-19 in hospitalized patients from 10 years of age who require supplemental oxygen.

2.6.2. Roxulitinib

Only preliminary data are available for roxulitinib. None of it is sufficient to support its use outside of studies [30].

2.7. Interferon

Interferons (IFN) have antiviral effects and modulate the immune response [64]. There are several case series, case-control trials, small RCT's and the interim results of the WHO-solidarity trial being published so far. Hung et al compared combination therapy including IFN ß-1b, ribavirin and lopinavir-ritonavir (n=86) vs lopinavir-ritonavir alone (n= 41) in an open label RCT [65]. Only 52 patients starting therapy <7d of symptom onset received at least one dose of interferon, as by study protocol. 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 ICU admission, although the study was probably underpowered for this [66]. 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 [67]. 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. Results from the WHO-SOLIDARITY trial show that Interferon IFN ß-1a given with or without lopinavir/ritonavir, resp 1412 and 651 patients, did not provide any survival benefit vs control, HR

1.16 (0,96-1,39) in hospitalized patients [25]. Recently two small studies have looked at the effect of early single dose administration of peginterferon-lambda in outpatients with COVID-19 and found opposing results [68,69]. A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions [70,71]. At this moment one small, underpowered RCT looked at the effect of combination of inhaled interferon ß-1b and Favipiravir vs standard of care with hydroxychloroquine in severe COVID-19, finding no effect [72]. Another pilot double-blind placebo RCT found that hospitalized COVID-19 patients treated with 14 days of nebulized interferon β-1a had a greater odds for clinical improvement [73]. No data were available on additional therapies used in these patients. Further studies are needed to clarify the role of Interferons in the treatment of COVID-19.

2.8. Chloroquine and hydroxychloroquine

Main message: Based on preclinical observations and the reported trial results it has been decided since the beginning of June (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore. In December 2020, the WHO recommended against the use of CQ/HCQ in clinical care regardless of COVID-19 severity.

Chloroquine and hydroxychloroquine inhibit 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 [31], but possibly in the intracellular compartment. This drug (not available in Belgium since 2015) has been used for decades (at a total of 25 mg/kg within 3 days) for malaria treatment without any monitoring and side effects, including in pregnant women. However, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages in patients with co-morbidities and co-medication.

Hydroxychloroquine (HCQ, drug marketed in Belgium as Plaquenil®) has appeared to be more potent than chloroquine *in vitro* (EC50=0.72 µM), so that lower dosages (than initially recommended) could be used [32]. 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 [33–37]. 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 [38–41]. 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. For the same reason (absence of efficacy in hospitalized patients), the SOLIDARITY trial 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. The results of the large RECOVERY trial on HCQ efficacy in hospitalized COVID-19 patients have demonstrated that mortality at Day 28 was similar in HCQ recipients compared to standard of care (421/1561, 27% versus 790/3155, 25%; p=0.15). No benefit was observed for all secondary outcomes and subgroups of patients [42]. Another smaller RCT in Brazil conducted in mild-to-moderate hospitalized patients did not find any improvement of the clinical status (seven-level ordinal scale) in participants having received HCQ (total dosage: 5600 mg), alone or with azithromycin (500 mg/day for 7 days) [43].

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 [44]. 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 [45]. A cluster-randomized trial by the same Spanish group did not show any reduction in the incidence of SARS-CoV-2 infection nor symptomatic COVID-19 when HCQ was used in post-exposure prophylaxis in healthy persons exposed to a PCR-positive case patient [46].

Meanwhile, several preclinical studies have not demonstrated any antiviral effect of HCQ in animal models (hamsters, macaques, including one study from the KUL [47–50].

2.9. Lopinavir/ritonavir

Main message: Due to lack of evidence for clinical benefit in the SOLIDARITY, RECOVER and DisCoVeRy trials, we no longer suggest off-label LPV/r as an alternative in severe COVID-19 disease. In December 2020, WHO recommended against the use of LPV/r in clinical care regardless of COVID-19 severity.

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-CoV-2 but also SARS-CoV-1 (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) [51]. 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 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 [52]. The results of the large RECOVERY trial in hospitalized patients with COVID-19 confirmed that lopinavir/ritonavir had no beneficial effect on mortality at day 28 (374/1616, 23% versus 767/3424, 22%, p=0.60) nor on any secondary endpoint (duration of hospital stay, progression of disease) [53]. Specific communication regarding ongoing clinical trials is still awaited.

2.10. Favipiravir

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 [54]. 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) [55]. 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 [56]. Favipiravir has not been selected for these recommendations, as this molecule is not available in Belgium outside clinical trials. An antiviral effect has been observed in animal models (hamsters) at high dosage [49]. This observation has been confirmed in another experiment in Syrian hamsters [57]. An interim analysis of a small phase 2 trial showed a lower rate of PCR positivity at day 5 post-favipiravir initiation but no difference at day 10 [58]. A multicentric RCT in Iran did not show any clinical benefit in hospitalized COVID-19 patients treated with favipiravir when compared to LPV/r [59]. Larger trials are still ongoing.

2.11. Molnupiravir

Molnupiravir is a new antiviral with demonstrated activity against SARS-CoV-2 in ferret and mouse models (in prophylaxis and treatment). After preliminary phase 1 and phase 2 data suggest the drug is safe and has antiviral activity in human as well, a phase 3 trial has been initiated in non-hospitalized patients. Results will not be known before the end of the year.

2.12. Camostat mesylate

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 [60]. Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (eg. NCT04355052 (Israel), NCT04321096 (Denmark)). The first results of the Danish RCT among 205 hospitalized patients (137 treated with camostat mesylate, 200 mg t.i.d. for 5 days, vs 68 treated with placebo) shows that this drug was safe, but had no viral nor clinical added benefit compared to standard of care [61]. The results of early treatment in ambulatory patients are still awaited. The drug is not commercially available in Belgium. A phase 2 trial in ambulatory patients looking for antiviral activity is ongoing in UZ Gent (Table 3). Large multi-country trials with clinical endpoints are ongoing and a trial is approved in the ambulatory setting in KUL.

2.13. Azithromycin

Azithromycin, shown to have some antiviral and immunomodulatory effect, has been promoted by some groups based on observational viral and clinical data [62]. The potential benefit of using AZM alone or with other drugs has not been demonstrated so far. Two large RCTs in Brazil have explored the usefulness of this drug in association with HCQ, both in mild/moderate [43] and severe hospitalized patients [16], and did not find any added value compared to HCQ alone. The azithromycin arm of RECOVERY was closed on November 27, 2020 for futility, after 2582 patients were randomized to azithromycin and compared to 5182 patients receiving standard of care. No effect was observed on 28-day mortality, nor on the risk of progression to mechanical ventilation or on length of hospital stay [63]. The results of DAWN-AZITHRO are also expected soon (Table 3).

2.14. Ivermectin

Main message: Many of the available RCTs show several methodological issues such as small sample size, lack of blinding, various drugs in the control arms, different clinical scenarios (as prophylaxis, early outpatient administration and later treatment in admitted patients) and/or incomplete data on outcomes, as summarized in a Commentary in the British Medical Journal (BMJ) Evidence-Based Medicine [114]. Therefore, the quality of the evidence does not seem to offer a sufficient robust base to justify the use or approval of ivermectin. The WHO and EMA recommend against the use of ivermectin in clinical care.

In vitro inhibition of SARS-CoV-2 replication in Vero/hSLAM cells9 28 has been reported with ivermectin (IVM), but at concentrations 50- to 100 times higher than those clinically attainable in human patients (150-400 µg/kg). *In vitro* high doses should not however be compared as such with plasma concentrations, as the distribution volume of ivermectin is very high. Preprint results from a study in the hamster model (Pasteur Institute) indicate that IVM is associated with less severe disease related to decreased production of pro inflammatory cytokines and increased levels of IL-10. Preliminary evidence based on compilation of observational studies suggested survival benefit in ivermectin recipients remaining significant after adjustments (OR, 0.27; 95% CI, 0.09-0.80; P< 0.03) [104]. Until now, four small (3 double-blind) randomized controlled trials (DB-RCT) studying the effect of ivermectin at different dosages on viral clearance and/or clinical recovery and/or survival have been published in peer-reviewed journals [105–109]. All four trials excluded severe and critical COVID-19 patients and dosages of ivermectin varied between 100 µg and 400 µg/kg. Two of them showed a more rapid decline in viral load but none of these studies demonstrated any differences in resolution of symptoms or in mortality between the ivermectin and placebo-treatment groups. Another small RCT in Israel, not yet peer-reviewed, suggested a lower proportion of viral shedding and viable cultures at day 6 in 47 patients early treated with IVM compared to 42 given placebo (38% versus 50% and 13% versus 48%, respectively; p=0.08); no clinical information was provided [110]. Two recently published RCTs failed to demonstrate any beneficial effect of ivermectin on (time to) symptom resolution. [111,112]. The first one evaluated in Colombia the administration of 300 µg/kg/day for 5 days of IVM in 200 mild COVID patients (vs 200 placebo) within 7 days after symptom onset; the second one evaluated 42 mg IVM in total (over 3 days) in 62 admitted patients in Brazil. A pre-print/not-peer reviewed preliminary meta-analysis of 18 RCTs on 2282 patients got a lot of publicity and suggested a 75% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus "control treatment" [113]. Specific communication regarding ongoing clinical trials is still awaited.

2.15. Colchicine

This well-known drug used in several inflammatory diseases has also gained much attention recently. No antiviral activity against SARS-CoV-2 has been demonstrated so far, but its inhibitory action against neutrophil chemotaxis/adhesion and against the inflammasome appears interesting [115]. A large multicenter placebo-controlled RCT evaluated colchicine (2 x 0.5 mg for 3 days followed by 0.5 mg/day for one month) in > 4000 PCR-confirmed COVID-19 ambulatory patients with risk factors for severe covid (being age, main comorbidities, fever or a set of full blood count abnormalities) [116]. The trial showed no significant effect of colchicine on the combined primary outcome (death or hospitalization) when considering all included cases (4,7% vs 5,8%, OR 0,79, p=0,081) but showed a reduction of this outcome when considering the prespecified group of PCR-proven cases (4,6% vs 6%, OR 0,75, p=0,042). There were two times more diarrhea in the colchicine group than in the placebo group (13.7 vs 7.3%; p<0.001). The trial was stopped at 75% of planned

recruitment, due to organizational constraints. As discussed in the accompanying editorial, these findings do not imply that colchicine will likely become the first-line community treatment for early COVID-19, because the effect size was small, and the number needed to treat large (70). It adds however some evidence that anti-inflammatory drugs administered early in the course of the disease may be beneficial [117]. For in-hospital patients, evidence remains scarce. A few observational studies using variable drug dosages have been published, suggesting a possible clinical benefit [118]. One small open-label RCT has evaluated the efficacy of colchicine for hospitalized patients (one third of the patients however did not require oxygen at inclusion) [119]. No patient received corticosteroids as part of SOC treatment. The trial showed a significant reduction in clinical deterioration and an improvement in terms of time to clinical deterioration in the colchicine group. It should be noted that recruitment was terminated prematurely due to slow patient accrual, with 105 of 180 planned inclusions. A second RCT including 75 moderately to severely ill patients (a majority of them also treated with corticosteroids) showed a reduction of the duration of both oxygen supplementation and hospitalization among colchicine-treated patients. ICU admission and death were rare in both groups [120]. Two systematic reviews of eight studies (some of them pre-print) with heterogeneous design and varied "control" arms both in out- and inpatients suggested some survival benefit and concluded that large RCTs were still needed. The current evidence does not permit to recommend for or against use of colchicine in the treatment of COVID-19 until data of larger RCTs are published. Of note, the RECOVERY consortium has announced by press release on the 5th of March 2021 that they have closed recruitment in the colchicine arm because it did not demonstrate mortality benefit in addition to corticosteroids in patients hospitalized with COVID-19. Peer-review publication is awaited.

2.16. Aspirin

Aspirin is a non-selective inhibitor of COX-1 and COX-2 enzymes leading to a decreased production of prostaglandins, thromboxane A2 by platelets. Low dose ASA is associated with antithrombotic effect. In animal models ASA inhibits disseminated intravascular coagulation (DIC) during *Staphylococcus aureus* sepsis through inhibition of platelet activation. Patients with septic shock have decreased risk of DIC when using ASA [121]. One retrospective study found a decreased risk of mechanical ventilation, ICU admission and in-hospital mortality among patients admitted with COVID-19 [122]. Different cohort studies have shown a decreased risk of acute lung injury/ARDS in patients on chronic ASA-treatment. Dozens of RCTs are evaluating ASA in COVID-19 in addition to standard of care. Notably the RECOVERY trial has already included >6000 patients in the ASA arm (150 mg daily + standard of care).

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 [123,124]. An RCT found no impact of ACEi/ARB switch in COVID-19 [125]. 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. A nationwide cohort study in Denmark found no difference in COVID-19 outcome in patients with recent use of NSAID [126]. However, to be safe, 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 in common practice) 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) [127]. Remdesivir is available for compassionate use in pregnant women with severe disease and the first observational data provide reassurance about safety [128]. International guidelines are available, including from NIH, RCOG and WHO guidance.

Note – children :

Specific guidelines are available: *Traitement et prise en charge de l'enfant atteint de la COVID-19: Particularités pédiatrique/Opvang en behandeling van kinderen met COVID-19 gerelateerde ziekte* (online on 1 December 2020):

FR: https://covid-19.sciensano.be/sites/default/files/Covid19/Guideline%20traitement%20COVID%20enfants.pdf

NL: https://covid-19.sciensano.be/sites/default/files/Covid19/Guideline%20behandeling%20COVID%20kinderen_0.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 important risk factors for 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 – Ambulatory care :

- **Treatment of COVID-19 patients in nursing homes :** Collège de Médecine Générale : Mise à jour du protocole thérapeutique des résidents d'institutions âgés de plus de 75 ans atteints de Covid-19 :

  https://www.le-gbo.be/wp-content/uploads/2020/10/20201025_Revision_Protocole_therapeutique_COVID_institution.pdf

- **Superior Health Council advice on Vitamine D, Zinc and COVID-19**

  https://www.health.belgium.be/fr/avis-9620-vitamine-d-zinc-et-covid-19

- **Outpatient care for Covid-19 patients in the context of saturation in Belgian hospitals**

  FR : https://kce.fgov.be/fr/soins-ambulatoires-aux-patients-covid-19-dans-le-contexte-d%E2%80%99une-saturation-des-h%C3%B4pitaux-belges

  NL : https://kce.fgov.be/nl/ambulante-zorg-voor-covid-19-pati%C3%ABnten-in-het-kader-van-de-verzadiging-in-belgische-ziekenhuizen

3. Summary of efficacy data of selected antiviral drugs

Table 2 : Summary of available clinical evidence for treatment with neutralizing monoclonal antibodies (mAb) against SARS-CoV-2 spike protein

mAb, Company	Clinical Trial		Study group	Main results	NNT	EMA approval	Available in Belgium
Bamlanivimab (LY CoV555/LY3819253) Eli Lilly and Company	Monotherapy (IV)	BLAZE-1 phase 2 NCT04427501 [97]	Mild to moderate COVID-19, outpatients	Statistically reducing of VL on Day 11 for Ly CoV555 at 2800 mg dose (-0.53 log, p=0.02)	NA	No CHMP review 05/03/21 for IV use	No
	Combined with Remdesivir (IV)	ACTIV-3/TICO NCT04501978 [98]	Hospitalised patients without end-organ failure	Efficacy outcomes at Day 5 not statistically significant in the LyCoV555+ remdesivir vs placebo group	NA	Since April 16, bamlavinimab monotherapy is no longer recommended in the U.S due to resistant variants (link)	
Bamlanivimab (LY CoV555/LY3819253) **+** **Etesevimab** (LY CoV016/LY3832479) Eli Lilly and Company	Combination therapy (IV)	BLAZE-1 phase 3. NCT04427501 [99] BLAZE-1 phase 3 High Risk patients Unpublished: [100]	Mild to moderate COVID-19, outpatients Mild to moderate COVID-19, outpatients at high risk group	Statistically reducing of VL on Day 11 for combination treatment (-0.57 log p=0.01) Unpublished	NA	No CHMP review 05/03/21 for IV use	No
Casirivimab + imdevimab Regeneron Pharmaceuticals, Roche	Combination therapy (IV)	Phase 2/3 NCT04425629 [101]	Mild to moderate COVID-19, outpatients	Interim analysis: proportion of MAV in REGN-COV2 group through Day 29 (3% vs 6% in the placebo group) and MAV proportion for baseline seronegative patients (6% vs 15% in the placebo group)	33 11 (baseline seroneg. patients)	No CHMP review 26/02/21 for IV use	Since 19 May 2021, via government for IV use in mild to moderate COVID-19

		Phase 3 portion NCT04425629 Preprint: [102]	Mild to moderate COVID-19, high risk outpatients	71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29	45.5		(conditional use) (link)
		Phase 3 NCT04452318 (SC) Unpublished: link	Prevention in household contact positive SARS-CoV-2 (SC)	Unpublished	NA		
Sotrovimab (VIR 7831/GSK4182136) GlaxoSmithKline and Vir Biotechnology	Monotherapy (IV)	Phase 2-3 COMET-ICE NCT04545060 Preprint: [129]	Mild to moderate COVID-19 at high risk group	85% of reduction of hospitalization or death through Day 29 (1% vs 7%)	16.7	No CHMP review 21/05/21 for IV use	No
	Combined with bamlanivimab (IV)	BLAZE-4 NCT04634409 Unpublished	Mild to moderate COVID-19	Unpublished			
Regdanvimab Regkirona (CT-P59) Celltrion	Monotherapy (IV)	Unpublished: link	Adult with mild to moderate COVID-19	Proportion of hospitalization, oxygen requirement or death by day 28: CT-P59 40 mg/kg: 4.0% CT-P59 80mg/kg: 4.9%, pooled CT-P59: 4.4% vs 8.7% in the placebo group	21.3	No CHMP review 26/03/21	No

mAb : monoclonal antibody; NNT: number needed to treat; EMA: European Medicines Agency; IV: intravenous; VL: viral load; NA : not applicable ; CHMP: Committee for Medicinal Products for Human use; MAV: medically attended visit; SC: subcutaneous.

Table 3 : *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 [130]*; we try to summarize the relevant information for the selected drugs*

Drug	***In vitro* activity**			***In vivo* activity (animal models)**			**Clinical studies SARS-CoV-2 (non-exhaustive)**	**Mechanism of action**
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	SARS-CoV-1	MERS-CoV	SARS-CoV-2		
Remdesivir / GS5734 (Veklury®); Limited availability in Belgium	+++ [131,132]	+++ [131–134]	+++ [31]	+++ [135]	+++ [133]	++ [19]	NCT04292899: No significant difference in 5-day and 10-day treatment course [22]. Post-hoc analysis showed that patients receiving mechanical ventilation or ECMO may benefit from 10 days NCT04257656: Terminated: no survival benefit could be demonstrated [20] 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 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 [23]. NCT04315948: No impact on 28-day mortality, on risk of progressing to mechanical ventilation, or on the length of hospital stay [25] WHO recommends against RDV use (link)	Interactions with viral polymerase [131,134]
Chloroquine phosphate (CQ) Not marketed in Belgium. Available via import or as magistral preparation	+++ [136,137]	++ [138]	++ [31]	+/- [139]	-	-	Although in initial SOLIDARITY (WHO) protocol, the trial was only ever pursued with hydroxychloroquine	Fusion and un-coating blockade, by lysosomal alkalization [136,137];

(500mg CQ = 300mg chloroquine base); Used for malaria								Interaction with the ACE2 receptor [136]; "Immuno-modulation"?
Hydroxy-chloroquine (HCQ) (Plaquenil®); Used for lupus, rheumatoid arthritis	+/-? [140]	-	+++ [32]	-	-	- [49,50]	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) [141] Was under investigation in the SOLIDARITY (WHO), RECOVERY (UK) and DisCoVeRy (INSERM) trials, at high dosages (9600 mg in total over 10 days for the former two trials and 5600 mg in total over 10 days for the latter). All three trials stopped enrolling patients in hydroxychloroquine arm: no clinical benefit in patients hospitalized with COVID-19 (press releases). No demonstrated efficacy on mortality at Day 28 in RECOVERY [42] Strong recommendation against use by WHO (Dec 2020) [25]	Not fully elucidated but assumed to be similar to that of chloroquine
Lopinavir /ritonavir (Kaletra®); Used in HIV infection	+/- [142–144]	- [145]	-	-	+/- [133,146]	-	Weak efficacy for SARS-CoV-1; associated with ribavirin & cortico-steroids [144] NCT04252885: Negative results for hospitalized patients with mild/moderate COVID-19 [147]; NCT04345289: No clear viral or clinical benefit in an patients hospitalized in China with severe disese [51]	SARS-CoV-2 protease inhibition ?

							Discontinued in the SOLIDARITY because of lack of benefit (press release). Also discontinued in DisCoVeRy No demonstrated efficacy on mortality at Day28 in RECOVERY [53]. Strong recommendation against use by WHO (Dec 2020) [25]	
Favipiravir Used in Japan against influenza	Not studied	Not studied	++ * [31]	-	-	+ [49]	ChiCTR2000029600: Shorter viral clearance time and improved radiological evolution compared to lopinavir/ritonavir (non-randomized) [56] NCT04373733 (PIONEER): recruiting NCT04349241: Completed, no yet published	Inhibition of the activity of RNA dependent RNA polymerase (RdRp)[148,149]
	**at higher dosage than for influenza)*							
Camostat Used in Japan for reflux esophagitis and pancreatitis	++ [60]	++ [60]	++ [60]	++ [150]	-	-	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 [60]
Interferons	+ [151]	+ [151]	++ [64,152]	+ [152]	+ [153]	- [25]	3 RCT's with small number of patients (see text). Further studies needed	

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.

4. Clinical trials in Belgium

For an overview of all currently 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). Additional trials are currently being set up in Belgium. The table below briefly summarizes only ONGOING trials (already recruiting).

Table 4: Belgian COVID-19 Clinical Trials

PROTOCOL CODE / EudraCT n°	STUDY TYPE	INVESTIGATED PRODUCTS	PATIENT PROFILE	PRINCIPAL INVESTIGATOR/ COORDINATING CENTER
COV-AID 2020-001500-41 (completed)	Multicentric, randomized, factorial design, interventional study	Six arms: Anakinra (anti-IL1), Siltuximab (anti-IL6), Tocilizumab (anti-IL6) in monotherapy, double or single combinations; standard of care (SoC)	COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome	B. Lambrecht / UZ Gent
SARPAC 2020-001254-22 (completed)	Multicentric, randomized, open-label, interventional study	2 arms: Sargramostim (recombinant GM-CSF)) vs SoC	Acute hypoxic respiratory failure of COVID-19 patients	B. Lambrecht / UZ Gent
DAWN – azithro 2020-001614-38	Multicentric, randomized, open-label, adaptive, proof-of-concept clinical trial	2 arms: Azithromycin vs SoC (other arms can be included later)	COVID-19 PCR confirmed hospitalized patients	UZ Leuven
DisCoVeRy 2020-000936-23 Remdesivir arm stopped	Multicentric, randomized, open-label, adaptive clinical trial	2 arms: ~~Remdesivir~~ vs SoC	COVID-19 PCR confirmed hospitalized patients	M. Hites / Hôpital Erasme UCL St-Luc
DAWN-plasma (No IMP, therefore no EudraCT number) Recruitment is finished	Open-label randomized Multicenter Adaptive design	2arms: convalescent plasma vs SoC	COVID-19 PCR confirmed hospitalized patients	G. Meyfroidt/ UZ Leuven
REMAP-CAP 2015-002340-14	Randomized, embedded, multifactorial, adaptive platform trial	Antiviral therapy: No vs Kaletra Corticosteroid therapy:	COVID-19 PCR confirmed hospitalized patients	AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent

	for community acquired pneumonia, amended for COVID-19	No vs hydrocortisone 7d vs shock dependent hydrocortisone Immune modulation: No vs interferon-beta-1a vs anakinra (anti-IL1)		
DAWN-antico 2020-001739-28A	Randomized, open-label, adaptive, proof-of-concept clinical trial	3 arms: High prophylactic LMWH +/- anakinra*; Apronin (antifibrinolytic) +/- anakinra*; standard dose of LMWH * anakinra only for patients in hyper-inflammatory stage	COVID-19 PCR confirmed hospitalized patients	UZ Leuven
Biophytis – BIO101 2020-001498-63	Adaptive design phase 2 to 3, randomized, double- blind, multicentre clinical trial	2 arms: BIO101 (activator of Mas-receptor of the renin-angiotensin system) vs SoC	COVID-19 PCR confirmed hospitalized patients	UCL Namur St elisabeth AZ St Maarten (Mechelen)
ZILU-COV 2020-002130-33 (completed)	prospective, randomized, open-label, interventional clinical trial	2 arms: Zilucoplan (inhibitor of complement protein C5) vs SoC	COVID-19 PCR confirmed hospitalized patients	B. Lambrecht/UZ Gent
OSCAR (GSK) 2020-001759-42	Randomized, double-blind, placebo-controlled clinical trial	2 arms Otilimab (anti-GM-CSF) vs SoC	Patients with severe pulmonary COVID-19 related disease	GSK
MOT-C-204 (Inotrem) 2020-001504-24	Randomized, double-blind, placebo controlled, adaptive, exploratory clinical study	2 arms: Nangibotide iv (TREM1 inhibitor) vs placebo	Mechanically ventilated patients due to COVID-19 and with features of systemic inflammation	UCL St-Luc, ZOL
TJT2012 2020-002102-58	Prospective open-label P1/2 clinical trial	Mesenchymal stromal cells	Patients with severe COVID-19 requiring	CHU Liège

			supplemental O2	
ARGX-117-2001 (ArgenX) 2020-001546-19 (completed)	First-in-human, open-label P1 clinical study	ARGX-117 iv (Humanized antibody that blocks C2b)	COVID-19 hospitalized patients	UZ Gent
AT-527 (ATEA pharmaceuticals) 2020-002869-34	Randomized, double blind, placebo controlled, P2 trial	AT-527 (guanosine nucleotide prodrug) Vs placebo	Moderate COVID-19 patients with risk factors for poor outcomes	CHU St-Pierre, AZ St-Maarten (Mechelen)
ABX464-401 (Abivax) 2020-001673-75 Halted for futility	Randomized, double blind, placebo controlled,, P2/3 trial	ABX464 (antiviral) Vs Placebo	Mild-moderate COVID-19 patients with risk factors	UZ Gent, Erasme and CHU Saint-Pierre
COV-AAT 2020-003475-18	Randomized, placebo controlled, double blind Phase 2 study	2-arm: Camostat (antiviral, serine protease inhibitor) vs placebo	Ambulatory COVID-19 patients	UZ Gent
ETHIC trial 2020-003125-39	Open label, randomized, P3b trial	2-arm: Enoxaparin vs SoC	Ambulatory COVID-19 patients	F. Cools / Thrombosis Research Institute
AZD7442 2020-004356-16	Randomized, double blind, placebo controlled, Phase 3 trial	2-arm: AZD 7442 (cocktail of 2 mAb against SARS-CoV-2) Vs Placebo As pre-exposure prohlyaxis	Healthy adults	Astra Zeneca
CONVINCE 2020-002234-32	Open-label, randomized, Phase 4 trial	factorial 2x2 design: Edoxaban and/or colchicine VS No intervention	Ambulatory COVID-19 patients	P Vranckx (Jessaziekenhuis hasselt)
TRISTARDS (Boehringer Ingelheim) 2020-002913-16	Open label, randomized, sequential, parallel-group, adaptive PIIb/III trial	Alteplase (thrombolyticum) High or low dose + SoC vs SoC alone	Hospitalized patients with ARDS	ULB Erasme / HOSP St-Pierre
FITE19 (PTC therapeutics) 2020-001872-13	randomized, double-blind, placebo-controlled, PII/III study	PTC299 (antiviral) Vs placebo	Hospitalized COVID-19 patients	CHU St Pierre / Clinique St Pierre (Ottignies)

MIT-Co001-C101 2020-003403-33	Randomized, double-blind, placebo-controlled, phase 2 trial	Estetrol (E4) + SoC vs placebo + SoC	Hospitalized moderate COVID-19 patients	Erasme Hospital CHR de la Citadelle
C4611001 (Pfizer) 2020-003905-73	Phase 1b, 2-part, double blind, placebo controlled	PF07304814 (antiviral) iv vs placebo	Hospitalized moderate COVID-19 patients	Hôpital Erasme CHU Brugmann Institut Jules Bordet CHU UCL Namur C.H.R. de la Citadelle
PANAMO 2020-001335-28	adaptive randomized double blind placebo controlled Phase II/III	IFX-1 (immnomodulator: C5a blocker) + SoC vs placebo + SoC	Hospitalized Patients with severe COVID-19 pneumonia	UZA CHU Dinant Godinne UCL Namur Erasme
DAWN-camostat 2020-005911-27	Randomized double blind controlled trial phase III	camostat mesylate vs placebo	ambulatory COVID-19 patients	UZ Leuven
COVID-RESCAP 2020-001714-38	Randomized, placebo controlled, double blind, phase II	RESCAP (bovine alkaline phosphatase) vs placebo	Severe COVID-19 patients with acute respiratory insufficiency	Jesssa Ziekenhuis Hasselt / B. Stessels
SG018 2020-004743-83	Randomized, double-blind, placebo-controlled, phase III	SNG001 (IFN-β1a) vs placebo	Hospitalised moderate COVID-19 patients	CHU Liège – Sart Tilman AZ Groeninge Kortrijk CHR Citadelle Liège CHU Brugmann Brussels
CV43043 (Roche) 2020-005759-18	Randomized, double-blind, placebo-controlled phase III	RO7496998 (AT-527) vs placebo	Mild to moderate ambulatory COVID-19 patients	3 primary care physicians in BE (Roche: global.rochegenentechtrials @roche.com)
HOPECOVID-19 2021-000492-36	Randomized, double-blind, placebo controlled, phase II	Lactavir vs placebo	Ambulatory COVID-19 patients	UCL
EXEVIR0101 2020-005299-36	FIH, open label, SAD (part 1) Randomised, double blind, placebo controlled (part 2)	XVR011 (bivalent single domain antibody fragment) vs placebo	Hospitalised mild to moderate COVID-19 patients	UZ Gent CHU de Liège UZ Brussel AZ Sint-Maarten, Mechelen CHU Saint-Pierre
Terminated trials	• Antivirals for COVID-19 2020-001243-15 (itraconazole) • COVIDAM 2020-001417-21 • SANOFI 2020-001269-35			

5. Annexes

Annex 1: Availability of remdesivir

The medicine Veklury® (remdesivir) is available in the strategic stock, stored and distributed by a State-designated distributor. It is available to hospitals for patients that fill the criteria for use as defined in this guidance. Hospital pharmacists have been informed on the procedure to obtain Veklury.
The FAMHP closely monitors the evolution of stocks and, if necessary, places new order to ensure sufficient supply.
Veklury is registered for the treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg). For pregnant women and children <12y, compassionate use is possible.

Emergency Compassionate use procedure *(as stated in art 107/1 (link))*
For pregnant women and children <12y. 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.

If you have problems obtaining the medicinal products in this guideline, please contact
supply-problems@fagg-afmps.be

Annex 2: Safety profiles
Safety profiles can be found at www.BCFI.be (SKPs) , www.CBIP.be (RCPs) or via
https://geneesmiddelendatabank.fagg-afmps.be/
More information via www.ema.europe.eu (European Medicines Agency)

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

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