Recommendations for the use of early COVID-19 therapy and prophylaxis by the Swiss Society of Infectious Diseases (SSI)

November 28, 2022

Note

The current recommendations will be reviewed and updated by the panel as soon as new peer-reviewed data from the respective trials become publicly available. To ensure treatment and prophylaxis availability for those patients with the highest anticipated need and benefit, the criteria outlined below will generally need to be met to qualify for monoclonal antibodies (mAbs) or directly acting antivirals (DAA) therapy or prophylaxis**.** Most of the phase 3 trials were performed during the Delta waves of COVID-19 in unvaccinated patients, and a simple extrapolation to current Omicron (and future) variants might not be accurate. Real world data are however available and tend to support the use of these treatment options beyond the populations included in registration trials. Individualized descision with patients and multidisciplinary teams are encouraged if appropriate.

Several antiviral drugs may prevent hospitalization in outpatients (and inpatients with new nosocomial infection) with a SARS-COV-2 infection and high risk for progression to a severe COVID-19 disease and death. mAbs for treatment have been used in Switzerland since May 2021, initially casirivimab/imdevimab (Ronapreve®, IV formulation), then sotrovimab (Xevudy, IV formulation) and, more recently, tixagevimab/cilgavimab (Evusheld, IM and, by extension, IV formulation; prophylaxis as well). The efficacy of anti-SARS-CoV-2 neutralizing mAbs is altered or reduced by mutations of the RBD domain of the spike protein.

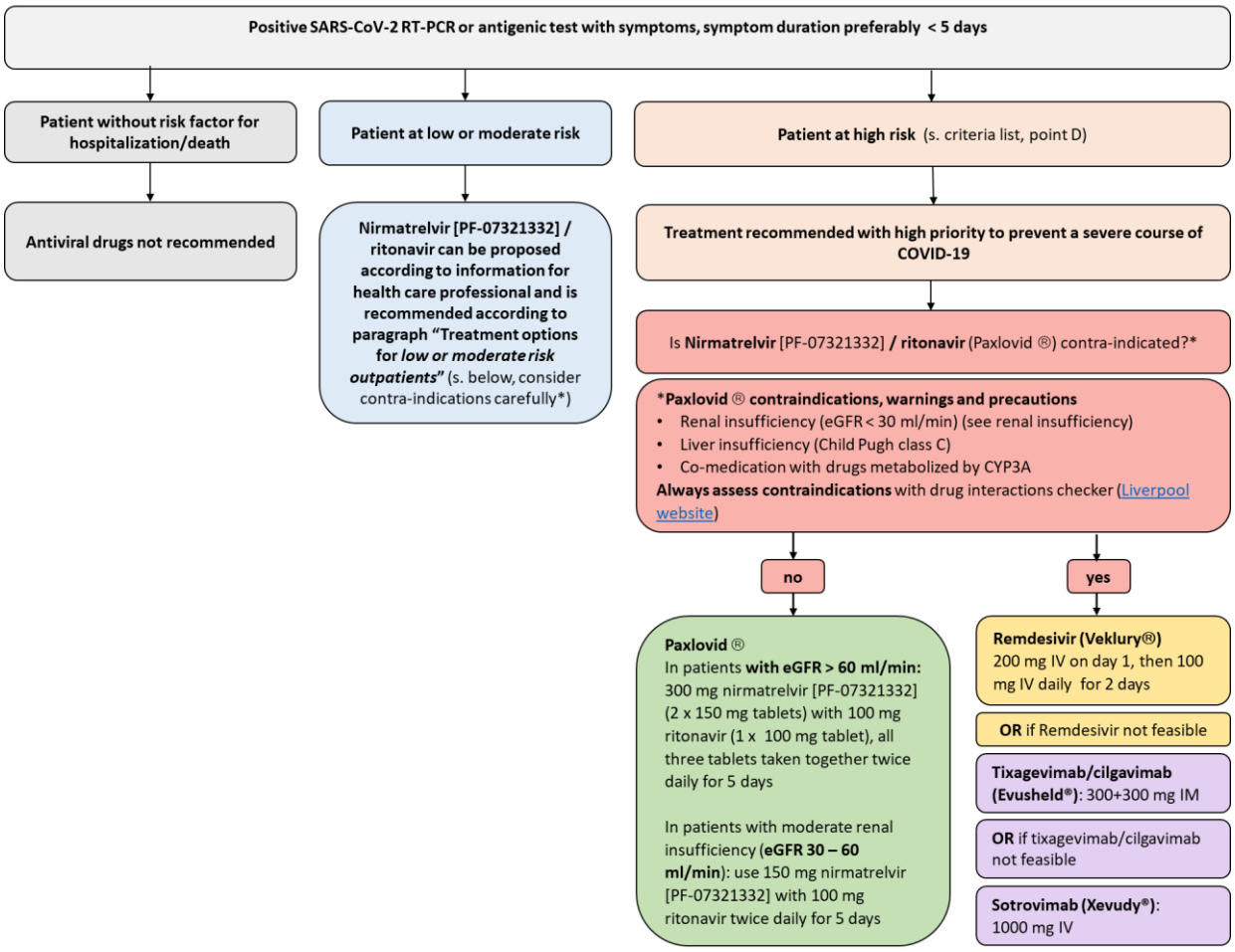
DAA such as nirmatrelvir [PF-07321332]/ritonavir (Paxlovid®, oral formulation), or remdesivir (Veklury®, IV formulation), have different mechanisms of action, and are all expected to retain activity against omicron strains. Antiviral therapy and prophylaxis have been associated with emergence of resistance, particularly in the immunocompromised host.

As shown in the decision tree (see below), in general, and in the absence of any contra-indications, we recommend **to prescribe nirmatrelvir [PF-07321332] /ritonavir (Paxlovid®) as a first line therapy for early treatment in at-risk outpatients to prevent a severe course of the COVID-19 disease.**

Nirmatrelvir [PF-07321332] / ritonavir (Paxlovid®) is the only available and approved oral DAA in Switzerland. If Paxlovid® is contra-indicated (mostly because of deleterious drug-drug interactions: see **COVID-19 drug interactions checker** (Liverpool website & Interactions with selected outpatient medicines and Paxlovid®), then IV remdesivir (200mg -100mg-100 mg over 3 days) can be prescribed in a similar indication.

In the absence of DAA option available or feasible, the mAbs tixagevimab/cilgavimab (highly dosed: tixagevimab 300 mg and cilgavimab 300 mg) or sotrovimab (highly dosed, 1000 mg) can be used as alternatives. Clinical evidence on mAb efficacy against BA.4 and BA.5 infections is scarce, but there are encouraging and convergent data « in real life » cohorts concerning immunocompromised patients in the Omicron era (mostly BA1) (Kertes J et al. CID 2022). At this point, Evusheld probably partly retains efficacy against BA.4 and BA.5 (cilgavimab component); sotrovimab efficacy is impaired to a similar extent as for BA.2 and, if used, should be used high dose (1000 mg). With sotrovimab also, efficacy data were surprisingly good in cohorts despite a neutralization loss against BA1 and BA2 in neutraliziation studies, demonstrating that the extrapolation of *in vitro* data to clinical efficacy is subject to discussion (Case JB et al. Nat Commun 2022, Martin-Blondel G et al. J Infect 2022, Wu et al. The Lancet Infectious Diseases 2022). BQ.1 is a SARS-CoV-2 sub-lineage of BA.5, which carries spike mutations in some key antigenic sites, including K444T and N460K. In addition to these mutations, the sublineage BQ.1.1 carries an additional spike mutation in a key antigenic site (ie R346T). *In vitro* data raises doubts on the clinical efficacy of mABs (Cao Y, et al. 2022), but clinical evidence against BQ.1 and BQ.1.1 infections is scarce.

Antiviral therapies for outpatients with SARS-CoV-2 infection



There will always be situations where patients cannot be allocated precisely. The decision in such cases should be discussed and made by the responsible multidisciplinary team.

A. OUTPATIENT TREATMENT

The following criteria describe high priority prescription of an early treatment and should all be fulfilled:

1. Adults and adolescents ≥ 12 years old and weighing ≥ 40 kg [1]
2. AND infection confirmed by antigenic test **or** PCR: a positive antigen test is sufficient to start the treatment, if the other criteria are met.
3. AND symptoms of COVID-19
4. AND within 5 days since onset of symptom (unless immune-suppressed individuals, in which case the delay since symptoms onsets can be less stringent)
5. AND eligibility according to the high risk group listed under D

[1] This age and weight limit is included in the approved HCP information for Xevudy and Tixagevimab/Cilgavimab but not in the HCP information for Paxlovid® and Veklury®. The decision to use Paxlovid® and Veklury® in adolescents ≥ 12 years old and weighing ≥ 40 kg must therefore be taken by the responsible multidisciplinary team.

Recommended treatment options for *high risk outpatients* to prevent a severe course of COVID-19

1) Nirmatrelvir [PF-07321332] / ritonavir (Paxlovid®):
300 mg nirmatrelvir [PF-07321332] (2 x 150 mg tablets) with 100 mg ritonavir (1 x 100 mg tablet), with all three tablets taken together **twice daily for 5 days** per os, unless contraindicated.

Contraindications, warnings and precautions for nirmatrelvir [PF-07321332] / ritonavir (Paxlovid®):

- Liver insufficiency (Child Pugh Class C)
- Co-medication with drugs metabolized by CYP3A.

To assess for contra-indications, use the **COVID-19 drug interactions checker** (Liverpool website & Interactions with selected outpatient medicines and Paxlovid®) in all situations when Paxlovid® is prescribed**.**

Renal insufficiency / Dialysis

- In patients with **moderate renal insufficiency** (eGFR 30 - 60 ml/min):
  - Day 1-5: 150 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir (Paxlovid®) twice daily
- **Renal insufficiency** (eGFR < 30 ml/min): Paxlovid® should not be used according to labelling, but in exceptional cases after decision in the multidiciplinary team the following dosing can be proposed **(off label use):**
  - Day 1: 300 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir (with all three tablets taken together)
    Day 2-5: 150 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir once daily
- **Dialysis patient:** Paxlovid® should not be used according to labelling, but in exceptional cases after decision in the multidiciplinary team the following dosing can be proposed **(off label use):**
  - patients > 40kg: Day 1: 300 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir (with all three tablets taken together)
    Day 2-5: 150 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir once daily, given after dialysis
  - patients < 40kg: Day 1: 150 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir
    Day 3 and Day 5: 150 mg nirmatrelvir [PF-07321332] / 100 mg ritonavir, given after dialysis

Treatment of pregnant women can be considered upon decision by a multidisciplinary team. Please refer to the information for healthcare professionals.

2) Remdesivir (Veklury®)
200 mg Day 1, 100 mg Day 2, 100 mg Day 3 IV. This three-day early treatment has been proven efficient in reducing hospitalisations in one study, but no impact on mortality was observed.

Only if no other option is feasible or available and with an infectious diseases consultation, taking circulating variants in the region into account :

3) Monoclonal Antibodies

a) Tixagevimab/cilgavimab (Evusheld)[2]: 300 mg Tixagevimab + 300 mg Cilgavimab IM for the current Omicron variants. A documented negative serology is advised. An IV application is possible in special situations upon decision by a multidisciplinary team[3].

[2] Tixagevimab/cilgavimab (Evusheld) is currently only approved by Swissmedic for pre-exposure prophylaxis but not for therapy.
[3] Intravenous administration is not included in the information for healthcare professionals of Evusheld.

OR

b) Sotrovimab (Xevudy) 1000 mg IV., i.e. double dose[4] for the current Omicron variants. A documented negative serology is advised.

Important note:

Because of reduced or absent *in vitro* neutralization efficiency of sotrovimab and of tixagevimab / cilgavimab against BQ.1 and descendant lineages containing mutations such as R346X (e.g. BQ.1.1), it is expected that the available mAbs in Switzerland may no longer be effective in most clinical situations, if such strains become dominant. The viral dynamics are followed very closely, and depending on the future epidemiology, the recommendations will be adapted.

Treatment options for *low or moderate risk outpatients*

Some other diseases or conditions are also associated with an increased risk of severe COVID-19 such as:

1. Any patient above 75 years old regardless of vaccination status or comorbidities
2. Age above 60 **and** incomplete vaccination scheme (no booster dose since more than 9 months)[5] **regardless of co-morbidities**
3. Age above 60 **and** significant co-morbidities **regardless the vaccination scheme**
4. Patients of any age with significant co-morbidities (cardio-vascular risks factors, chronic lung disease, trisomy 21, overweight [BMI 30 or higher] etc.) **and** incomplete vaccination scheme (no booster dose since more than 9 months)[5]

Nirmatrelvir [PF-07321332] /ritonavir can also be proposed as first line antiviral in this population according to the information for health care professionals, for example in the presence of severe symptoms, incomplete vaccination scheme, multiple co-morbidities and transmission risks as evidence for efficacy also in the recent era have been confirmed.

B. INPATIENT TREATMENT

For inpatient recommendations see SSI guidelines.
Remdesivir can also be used up to 7 days since symptom onset, in hospitalized patients with pneumonia according to the information for healthcare professionals (different indication than for outpatients).

Note: For patients hospitalized for reasons unrelated to COVID-19, who newly test positive for SARS-CoV-2 in the hospital, treatment criteria outlined in section A, OUTPATIENT TREATMENT apply.

C. PRE-EXPOSURE PROPHYLAXIS

Passive immunisation therapy is primarily given to patients who belong to the **high risk group as** listed below (D) who, in addition, fulfil one of the following criteria:

a) Failed to mount an anti-Spike-IgG antibody response (i.e. an absent or nearly absent antibody test) after vaccination with at least three doses of a SARS-CoV-2 vaccine approved in Switzerland (preferably an mRNA vaccine), and a fourth dose is not expected to increase the antibody level. The antibody titre should be measured within four weeks after the last vaccine dose.

OR

b) Who cannot be vaccinated owing to their inability to establish vaccine protection due to allogeneic HCT, CAR-T therapies, or B-cell-depleting therapies in the previous < 3 months.

[4] This dosis is not included in the information of Xevudy (Sotrovimab) for health care professionals. The decision to this off-label use must therefore be taken by the responsible multidisciplinary team.
[5] Regardless of the vaccine type

Tixagevimab/cilgavimab (Evusheld) should be used as an IM administration of 300 mg tixagevimab and 300 mg cilgavimab[6] as two separate, sequential intramuscular injections with repeated doses every six months for as long as SARS-CoV-2 circulates. An IV application is possible in special situations upon decision by a multidisciplinary team[7].

Because of reduced or absent *in vitro* neutralization efficiency of tixagevimab / cilgavimab against BQ.1 and descendant lineages containing mutations such as R346X (e.g. BQ.1.1), it is expected that the mAB combination may no longer protect from COVID-19, if such strains become dominant. Therefore, patients should be advised to maintain protective measures, including mask-wearing and hand hygiene in addition to the use of pre-exposure prophylaxis. Persons at risk should be tested and treated as early as possible in case they develop COVID-19 symptoms. The viral dynamics are followed very closely, and depending on the future epidemiology, the recommendations will be adapted.

Of note, Evusheld can be prescribed 2 weeks after a SARS-CoV-2 vaccine if appropriate. After Evusheld administration, SARS-CoV-2 vaccination should be delayed for at least 3 to 6 months. Of note, due to the partial protection of Evusheld, in the presence of compatible symptoms, SARS-CoV-2 diagnosis tests should be performed without delay.

D. High risk group eligible for early DAA, antibody treatment or prophylaxis

- HIV-infection with a CD4+ T cell number of < 200 per µl
- Hereditary immunodeficiencies
- Anti-CD20 or Anti-CD19 monoclonal antibody treatment or other B-cell depleting therapies, Bruton-tyrosine kinase inhibitors, including immunosuppressive therapies (particularly with long-term use of glucocorticoids >20mg prednisone equivalent/d or cancer on chemotherapy)
- Hematological malignancies (e.g., leukemia, lymphoma, GVHD; including autologous and allogeneic HSCT and CAR-T, multiple myeloma, myeloproliferative diseases) with neutropenia (< 1'000 neutrophils/µl for ≥ 1 week) or undergoing active therapy or after HSCT
- Sickle-cell disease
- Solid organ transplant recipients

[6] This dose is higher than reported in the information for healthcare professionals of Evusheld and the phase III preventive trial. The higher dose is more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1.1, Omicron BA.2). Other dosages than recommended in this criteria list should be decided by a multidisciplinary team.
[7] Intravenous administration is not included in the information for healthcare professionals of Evusheld.