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

December 12, 2023

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 availability for those patients with the highest anticipated need and benefit, the criteria outlined below will generally need to be met to qualify for direct acting antivirals (DAA) therapy**.** Most of the registrational 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 largely available and have confirmed the use of these treatment options beyond the populations included in registration trials. Individualized decision 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.

DAA such as nirmatrelvir /ritonavir (Paxlovid®, oral formulation), or remdesivir (Veklury®, IV formulation) do retain activity against most recent strains.

Antiviral therapy and prophylaxis have been associated with emergence of resistance, particularly in the immunocompromised host, and particularly with a drug that is not approved in Switzerland, such as molnupiravir.

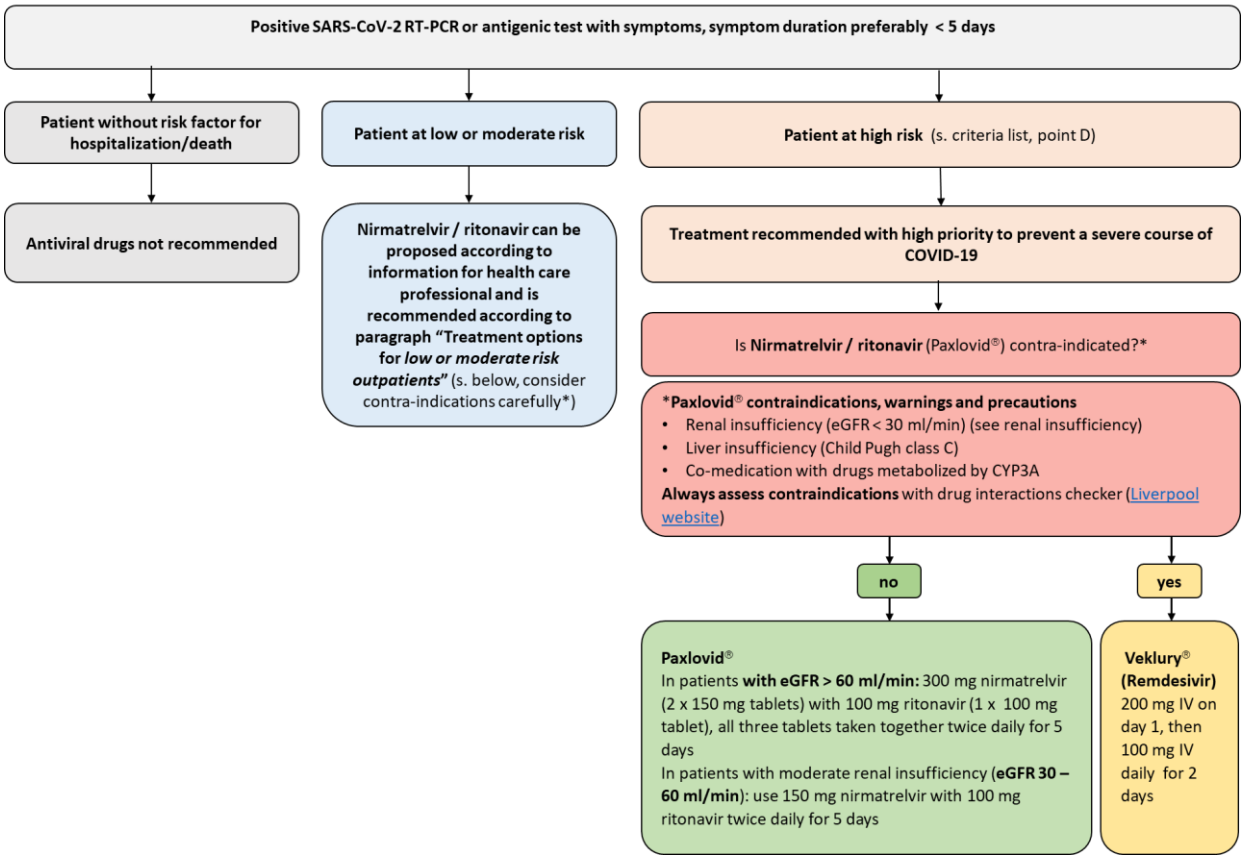
As shown in the decision tree (see below), in general, and in the absence of any contra-indications, we recommend **to prescribe nirmatrelvir /ritonavir (Paxlovid®) as a first line therapy for early treatment in at-risk outpatients to prevent a severe course of the COVID-19 disease.**

Nirmatrelvir / 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.

Although different SARS-CoV-2 variants are co-circulating in Switzerland, they are mostly a variation of XBB sublineages present at the moment. Clinical evidence on monoclonal antibodies (mAb) efficacy against XBB derived omicron strains (including EG.5) is scarce, while *in vitro* neutralization data is often available. Sotrovimab (Xevudy®) efficacy can be anticipated from *in vitro* data in the current epidemiological situation, but it has not been confirmed in the clinical setting. Routine application of mAbs in the clinical setting is therefore currently not indicated.

Additional information regarding ordering and invoicing of available drugs can be found here.

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. Infectiology specialized consultation should be seeked, when none of these options is available.

A. OUTPATIENT TREATMENT

The following criteria describe the 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] According to the approved HCP information, Paxlovid® is indicated for adult patients and Veklury® for adult and pediatric patients (with a body weight of at least 40 kg) in the outpatient setting. The decision to use Paxlovid® 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 / ritonavir (Paxlovid®):
300 mg nirmatrelvir (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 / 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 / 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 / 100 mg ritonavir (with all three tablets taken together)
    Day 2-5: 150 mg nirmatrelvir / 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 / 100 mg ritonavir (with all three tablets taken together)
    Day 2-5: 150 mg nirmatrelvir / 100 mg ritonavir once daily, given after dialysis
  - patients < 40kg: Day 1: 150 mg nirmatrelvir / 100 mg ritonavir
    Day 3 and Day 5: 150 mg nirmatrelvir / 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.

- **Renal insufficiency** (eGFR < 30 ml/min): Remdesivir (Veklury®) does not need to be adapted to renal insufficiency, according to FDA and EMA approval. Please be aware that this is an off-label use in Switzerland.

Important note:

There is no space for routine therapeutic mAb in Switzerland in the current circulating strain era and based on the current knowledge. However, in very rare and specific situations, if nirmatrelvir / ritonavir (Paxlovid®) or remdesivir (Veklury®) are not indicated, sotrovimab (Xevudy®) can be considered by specialists at a dose of 1000 mg[2]. This guidance will regularly be adapted.

For immunosuppressed patients, an academic-led clinical trial is currently recruiting and does test the efficacy of a combination of antivirals, with or without a prolonged duration of 10 days for nirmatrelvir / ritonavir.

[2] This dosis is not included in the information of sotrovimab (Xevudy®) for health care professionals. The decision to this off-label use must therefore be taken by the responsible multidisciplinary team.

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** unvaccinated **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 35 or higher] etc.) **and** incomplete vaccination scheme (no booster dose since more than 9 months)

The benefit/risk has to be weighted against the limited number of hospitalized patients with severe pneumonia in this group. Nirmatrelvir / 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 a COVID-19 related 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

The use of monoclonal antibodies for COVID prevention is currently not recommended until there are proven and effective antibodies available for the circulating SARS-CoV-2 strains.

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