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Opinion of the AvATher group on ENSITRELVIR (Xocova®)

Response to the request from the Directorate General for Health (DGS) regarding the evaluation of the potential role of ensitrelvir in the therapeutic and prophylactic arsenal against COVID-19

13 November 2025

Mandate:
The DGS mandated the AvATher group to assess the potential interest of ensitrelvir for the treatment and prevention of COVID-19 in France. This mandate follows the intention of the Japanese owner of the molecule to explore its relevance in several European countries before submitting a Marketing Authorisation Application at the European level.

Within this mandate, the DGS requested that the AvATher group determine whether the available clinical results are sufficiently robust and supported by a high level of evidence, and identify in which indications a clinical benefit could be demonstrated, both in post exposure prophylaxis and in the treatment of mild to moderate disease.

The DGS also requested clarification on whether a medical need exists that would justify making this drug available in France, in view of the therapeutic options already authorised and routinely used.

A. Overview of the SARS-CoV-2 epidemiological situation in France

In France, SARS-CoV-2 circulation remained low during the first half of 2025, with a limited number of virological detections and a moderate hospital impact. However, the most recent ERVISS surveillance data indicate a gradual increase in detections starting at the end of summer 2025, in a context where testing activity remains greatly reduced. As a result, the available data reflect trends rather than the actual magnitude of transmission. Despite this increase, COVID-19 related hospitalisations remain low and stable, with no notable pressure on emergency departments or critical care services. Genomic characterisation confirms the predominance of the **XFG** sub lineage, alongside the continued circulation of the **NB.1.8.1** sub lineage, with no indication of increased severity or significant immune escape[1,2].

Syndromic surveillance data from general practice for week 45 of 2025 confirm a low level of activity, with an estimated incidence of **10** cases of COVID-19 per **100 000** inhabitants among consultations for acute respiratory infections. The proportion of samples testing positive for SARS-CoV-2 in the virological network was **7%** (8 out of 114), a decrease compared with the previous week. Individuals with COVID-19 seen in primary care had a median age of 49 years,

[1] https://erviss.org/
[2] https://www.santepubliquefrance.fr/content/download/769667/4858458?version=1

ranging from 6 months to 94 years. Most patients had no identified comorbidities, and hospital admission remained rare, occurring in only **0.6%** of cases.

Overall, the indicators point to moderate and stable viral circulation, with a limited clinical impact, in a context of high population immunity and low pressure on the health system[3].

B. ENSITRELVIR (Xocova®)

Ensitrelvir is an oral antiviral agent that targets the 3C-like protease of SARS-CoV-2, a key enzyme involved in the maturation of the viral polyproteins pp1a and pp1ab[4]. It differs from nirmatrelvir in that it does not require co-administration with ritonavir. However, ensitrelvir is itself a strong inhibitor of CYP3A4, which exposes patients to significant drug interactions, particularly when they are receiving multiple medications[5]. The recommended regimen consists of one daily dose for five days[6]. In 2022, ensitrelvir received an emergency approval in Japan for the treatment of mild to moderate forms of COVID-19[7], regardless of vaccination status or risk of severe disease. This emergency approval was granted based on the expected efficacy of Xocova and the acceptability of its safety profile, derived from results from the Phase 2 portion of a Phase 2/3 study (497 participants, combining Phase 2a and Phase 2b) and from the results of a Phase 3 study (1821 participants).

Clinical studies conducted in patients with mild to moderate COVID-19, including the Phase 3 **SCORPIO SR** trial[8] showed that ensitrelvir given within five days after symptom onset reduced the time to symptom resolution by approximately one day compared with placebo, while also inducing a rapid and significant reduction of viral load in the upper respiratory tract. These outcomes were associated with an overall acceptable safety profile. In the adaptive **PLATCOV** trial[9], ensitrelvir was directly compared with nirmatrelvir/ritonavir in terms of viral clearance rate. Both treatments accelerated the decline in viral load, with a slightly greater effect observed for nirmatrelvir/ritonavir. In addition, observational data from Japan in patients at increased risk suggest a reduced risk of hospital admission among subjects treated with ensitrelvir compared with those who received no antiviral therapy[10].

[3] https://www.sentiweb.fr/document/6697
[4] Ullrich S, Nitsche C. The SARS-CoV-2 main protease as drug target. Bioorg Med Chem Lett. 2020 Sep 1;30(17):127377. doi: 10.1016/j.bmcl.2020.127377.
[5] https://www.covid19-druginteractions.org/site_news/43
[6] https://www.fda.gov/media/155050/download
[7] https://www.shionogi.com/global/en/news/2022/11/e20221122.html
[8] Yotsuyanagi H, Ohmagari N, Doi Y, Yamato M, Bac NH, Cha BK, Imamura T, Sonoyama T, Ichihashi G, Sanaki T, Tsuge Y, Uehara T, Mukae H. Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19: The SCORPIO-SR Randomized Clinical Trial. JAMA Netw Open. 2024 Feb 5;7(2):e2354991. doi: 10.1001/jamanetworkopen.2023.54991.
[9] Schilling WHK, Jittamala P, Wongnak P, Watson JA, Boyd S, Luvira V, Siripoon T, Ngamprasertchai T, Batty EM, Beer E, Singh S, Asawasriworanan T, Seers T, Phommasone K, Evans TJ, Kruabkontho V, Ngernseng T, Tubprasert J, Abdad MY, Madmanee W, Kouhathong J, Suwannasin K, Pagornrat W, Piteekan T, Hanboonkunupakarn B, Poovorawan K, Potaporn M, Srisubat A, Loharjun B, Chotivanich K, Imwong M, Pukrittayakamee S, Dondorp AM, Day NPJ, Piyaphanee W, Phumratanaprapin W, White NJ; PLATCOV Collaborative Group. Antiviral efficacy of oral ensitrelvir versus oral ritonavir-boosted nirmatrelvir in COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial. Lancet Infect Dis. 2025 Oct 10:S1473-3099(25)00482-7. doi: 10.1016/S1473-3099(25)00482-7.
[10] Takazono T, Fujita S, Komeda T, Miyazawa S, Yoshida Y, Kitanishi Y, Kinoshita M, Kojima S, Shen H, Uehara T, Hosogaya N, Iwanaga N, Mukae H. Real-World Effectiveness of Ensitrelvir in Reducing Severe Outcomes in Outpatients at High Risk for COVID-19. Infect Dis Ther. 2024 Aug;13(8):1821-1833. doi: 10.1007/s40121-024-01010-4.

Regarding post-exposure prevention, the **SCORPIO PEP** trial[11] evaluated ensitrelvir in household contacts of an index symptomatic case within **72 hours** of symptom onset. Among participants confirmed negative at baseline, treatment reduced the risk of symptomatic infection by **67%** within ten days following exposure, with a stronger effect when treatment was initiated very shortly after exposure. The safety profile observed in prophylaxis was similar to that reported for treatment. These results suggest efficacy in reducing intrafamily transmission, while also highlighting that the benefit depends strongly on very early initiation, which limits its practical applicability outside highly controlled settings.

The potential role of ensitrelvir within the therapeutic options available in France has therefore been examined in light of these findings, taking into account the availability of nirmatrelvir/ritonavir, its limitations related to drug interactions, the reduced efficacy of monoclonal antibodies against the currently circulating sub lineages, and the needs of certain at-risk populations.

C. Recommendation of the AvATher group regarding ENSITRELVIR in the target population for COVID-19 prophylaxis

Based on the available data and discussions within the group, AvATher considers that the use of ensitrelvir for post-exposure prophylaxis cannot be recommended in the current epidemiological context.

Although the **SCORPIO PEP** trial reports a relative reduction of **67%** in symptomatic infections, the group emphasizes that the expected real public health impact would be low for several reasons:

- The study population was young, had few comorbidities, and is not representative of the groups that would be considered a priority in France;
- The study assessed only symptomatic infections, with no demonstrated effect on hospital admission;
- Given the very low level of viral circulation and hospital admissions, the number of severe cases that could be avoided would be extremely limited;
- Practical implementation of post-exposure prophylaxis would require very early identification of eligible contacts within 72 hours, which is difficult to achieve;
- The molecule itself has significant drug interactions through CYP3A, which would exclude a large proportion of very high-risk patients, including transplant recipients.

However, the group agrees that ensitrelvir could have a potential role in post-exposure prophylaxis in a different future scenario, in particular:

[11] https://shionogimedical.com/s3fs/s3fs-public/2025-03/Oral%20Presentation%20-%20SCORPIO-PEP%20CROI%202025.pdf?VersionId=KbQ4yJis8foCkR0Kgn89tPOld6dYIu54

- In the event of the **emergence of an immune escape variant causing a large epidemic wave and or associated with greater severity**, especially if resistance to acquired immunity from prior infection or vaccination increases;
- Or within a **preparedness strategy** for such a scenario, with **stockpiling as a complement to Paxlovid**, since the drug could be useful to reduce transmission within households or clusters.

At this stage, no positive recommendation can be made for the use of ensitrelvir in post-exposure prophylaxis. Its potential interest could only be considered in exceptional circumstances, as part of preparedness for a future resurgence with greater severity, and together with reinforced monitoring of antiviral susceptibility.

D. Recommendation of the AvATher group regarding ENSITRELVIR in the target population for the treatment of COVID-19

For the treatment of mild to moderate forms of COVID-19, AvATher considers that the available data do not justify the integration of ensitrelvir into the national strategy at this time.

Results from the **SCORPIO SR** program show a modest clinical benefit, limited to a reduction of about **0.6** day in the time to symptom resolution, with no documented decrease in the risk of hospital admission or progression to severe disease. The experts note that the trial mainly included young adults, often vaccinated, with very few patients who were truly at high risk, which considerably limits the applicability of the results to priority populations in France.

In addition, the drug interactions related to CYP3A inhibition, comparable to those observed with nirmatrelvir/ritonavir, represent a major barrier for polymedicated patients, particularly immunocompromised and transplant recipients. These are precisely the individuals for whom a clinical benefit would be most expected.

The group nevertheless highlights that, in the context of a preparedness plan for a possible future wave, ensitrelvir could be included as an additional antiviral, notably because:

- It has a mechanism of action similar to that of nirmatrelvir, and the two molecules hold a broadly comparable place in patient management;
- Their resistance profiles are complementary, as mutants escaping one molecule generally remain sensitive to the other;
- Neither antiviral would address a clinical need that the other could not meet, which supports an integrated approach within a broader preparedness strategy;
  This could include the possibility of conducting future comparative trials under real conditions (clusters, nursing homes, high risk patients) in order to clarify their relative positioning and respective usefulness in an evolving epidemic context.

Given the current epidemiological situation, characterized by low severity, low rates of hospital admission, and high population immunity, the group does not recommend the use of ensitrelvir for the curative treatment of COVID-19.

CONCLUSIONS

- Based on all available data, the AvATher group does not consider that **ensitrelvir has, at this stage, any role in the national strategy for the management of COVID-19**, whether for post-exposure prophylaxis or for the treatment of mild to moderate forms and even less for severe forms. The clinical efficacy observed in the trials remains modest, the study populations are not representative of the priority patients in France, and the constraints related to drug interactions significantly limit its use in the individuals at highest risk. In the current context of low viral circulation, limited hospital impact, and high population immunity, the introduction of **ensitrelvir does not respond to a public health need**.
- The group nevertheless considers that a **re-evaluation could be considered in a different epidemiological context, particularly in the event of the emergence of a more severe variant or a variant escaping immunity and causing an epidemic wave**, or within a limited preparedness perspective, given the potential virological complementarity between ensitrelvir and nirmatrelvir.
- Any future integration of the drug should, however, rely on **updated antiviral susceptibility data and on clinical trials conducted in populations that are truly at high risk**.

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