Handling Uncertainty in Health-Economic Assessments: Experience From COVID-19 in France

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OBJECTIVES

> This study aims to **describe how health economic analyses were assessed in France** to appraise COVID-19 treatments **in a context of parametric and structural uncertainty**.

> **Identify key areas of improvement for future health-economic evaluations** to be submitted at the French HTA body in the COVID-19 context.

METHODOLOGY

> Descriptive Review of economic opinions from the HAS (French HTA body) medico-economic commission (CEESP), published from January 2020 to June 1st 2023 on COVID-19 treatments. A focus on uncertainty management is made, considering epidemiological context and ability of modelling to quantify and explore uncertainty to guide decision making.

RESULTS

> **Four economic opinions** published by HAS on COVID-19 treatments were analyzed **concerning 3 treatments** (including prophylaxis) to prevent severe forms of COVID-19.

Table 1 – Economic opinions on COVID-19 treatments

Product	Indication	Date of CEESP opinion
EVUSHELD (tixagevimab/ cilgavimab)	Treatment of **adults and adolescents** (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are **at increased risk** of progressing to severe COVID-19.	March 14th 2023
EVUSHELD (tixagevimab/ cilgavimab)	**Pre-exposure prophylaxis of COVID-19 in adults and adolescents** aged 12 years and older weighing at least 40 kg	August 30th 2022
XEVUDY (sotrovimab)	Treatment of **COVID-19 in adults and adolescents** (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are **at increased risk** of the disease becoming severe.	July 19th 2022
PAXLOVID (nirmatrelvir/ ritonavir)	Treatment of **COVID-19 in adults** who do not require supplemental oxygen and who are **at increased risk** for progressing to severe COVID-19.	April 16th 2022

> **Economic modeling** relied on 1 Markov model (using DICE simulation), and three decision tree + Markov models, **all modeling ambulatory and hospital care for COVID-19, then long-COVID and death**.

> **No one modeled inter-individual transmissions** nor reinfections.

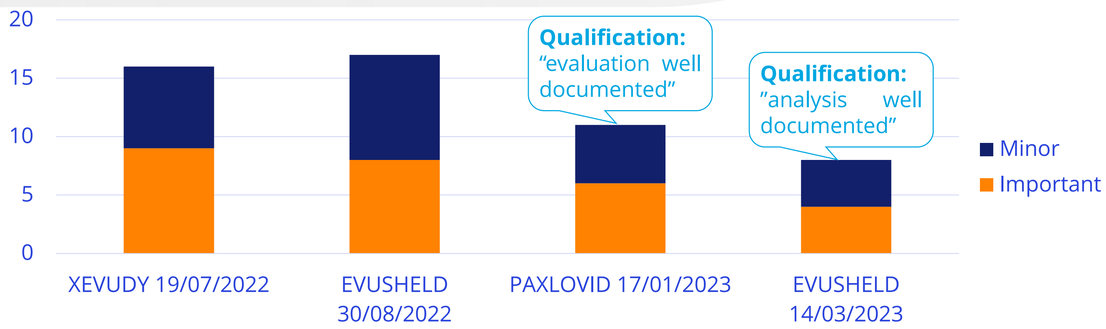

Figure 1 - Number of total methodological reservations by grade in each opinion

> **Main reservations** from CEESP concerned:

- Simulated population: 1 important reservation for **transposability of trial population** to current practice et epidemic situation for all opinions;
- Modeling: 1 important reservation due to the **lack of modeling of reinfections** for 3 opinions;
- Transition probabilities and extrapolations: a global **lack of details and discussion and heterogeneity of data sources** lead respectively to 2 important reservations (XEVUDY), 2 important and 1 minor reservation (EVUSHELD-2022), 1 important reservation (PAXLOVID) and 1 minor reservation (EVUSHELD-2023);
- Utility estimations: **heterogeneity of data sources and limited sensitivity analyses** + **plausibility of some values and assumptions**, lead respectively to 2 important reservations (XEVUDY), 1 important and 1 minor reservation (EVUSHELD-2022), 1 important reservation (PAXLOVID) and 1 minor reservation (EVUSHELD-2023);

> **Other inconsistencies** could be noted **in reservations across opinions**:

- Cycle length was criticized and conducted to important and minor reservation for XEVUDY and PAXLOVID;
- Test of confidence interval was missing in sensitivity analyses and led to important reservation in XEVUDY vs minor in PAXLOVID;
- Some reservations are duplicated for the same methodological item (test of infection rate in budget impact analysis for EVUSHELD-2022 leading to 2 reservations), unlike specified in CEESP's doctrine[1].

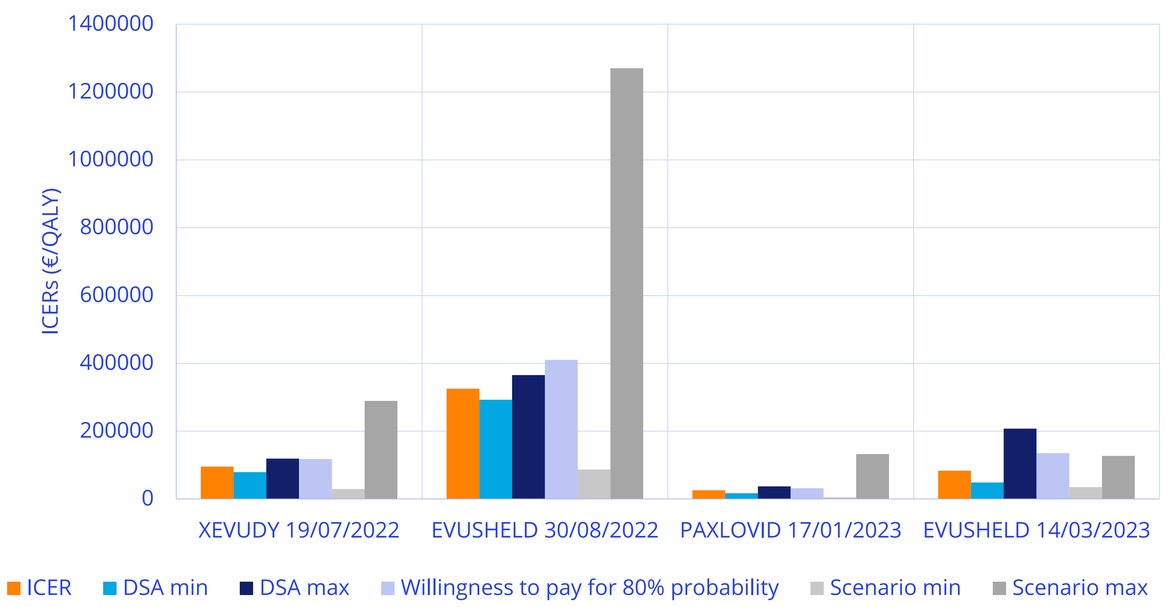

Figure 2 – Uncertainty exploration by COVID-19 treatments

> Uncertainty was explored through sensitivity analyses in opinions and was quite variable depending on the products (figure 2), PAXLOVID showing the lowest and most contained ICERs [5 218 - 132 301]. Whereas EVUSHELD in prophylaxis (30/08/2022) showed high variability. (Figure 2)

> However, **HAS' economic committee wasn't able to conclude on efficiency** of the products **due to global major uncertainty**. Global major uncertainty objected were based on the following:

- **Systemic uncertainty due to epidemiological context**: number and severity of epidemic waves, clinical data temporality and transposability, evolution of level of care through time and loss of efficacy of treatments.
- **Modelling and methodological uncertainty** due to assumptions made, considering lack of data and knowledge in the COVID-19 context.

> However, **the committee did not invalidate the methodology for any of the manufacturers' analyses**, neither for cost-utility analyses (N=4) nor budget impact analyses (N=4), and **for 2 opinions, analyses were qualified as "well documented"**.

CONCLUSION

> While modelling was used by Ministry of Health in the early COVID-19 pandemic to guide public health measure in France[2], **authorities now show stronger risk-aversion towards economic models' uncertainty**. HAS' clinical committee was able to conclude on COVID-19 treatments' efficacy, and other HTA agencies such as NICE[3] concludes on efficiency whereas HAS' economic committee did not. However **real-world data on COVID-19 are available to tackle parametric and contextual uncertainty**.

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