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[C2H2213] Summary of cost-effectiveness evaluation of ensitrelvir (Xocova®)

1. Indications

Coronavirus disease 2019 (COVID-19)

2. Price of the drug

Ensitrelvir has been reimbursed since March 2023 at JPY 7,407.40 (as of October 2024). The price was calculated based on the similar efficacy comparison method with a usefulness premium (II) of 5%. This product was designated as an H1 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

This product is indicated for the treatment of COVID-19. The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described below:

Population	Adults with mild to moderate COVID-19 (aged 18 years and older) (a) Without risk factors for severe outcomes* (b) With risk factors for severe outcomes* *The definition follows Clinical Management of Patients with COVID-19 by the MHLW version 9.0
Comparator	(a) Standard of care (SoC)* *Except other antiviral medications indicated for treatment of COVID-19 (b) nirmatrelvir/ritonavir

4. Evaluation of additional benefits

The manufacturer referred to data from clinical trials of ensitrelvir (Phase 2b and Phase 3 parts of T1221). The manufacturer conducted a subgroup analysis of T1221 and reported that the time to resolution of the five COVID-19 symptoms was shorter for ensitrelvir than for the placebo, and that the proportion of post-COVID-19 cases was smaller for ensitrelvir than for the placebo. Therefore, the manufacturer claimed an additional benefit of ensitrelvir over the SoC in population (a), without risk factors for severe outcomes. For population (b), with risk factors for severe outcomes, the manufacturer performed a network meta-analysis using the T1221 and EPIC-HR trials (trials for nirmatrelvir/ritonavir) and reported greater changes from baseline in viral RNA levels for ensitrelvir than for nirmatrelvir/ritonavir. The manufacturer therefore considered that ensitrelvir could be expected to be as useful as or better than nirmatrelvir/ritonavir but concluded that it had "no additional benefit" or "cannot be judged to have additional benefit."

The results of the systematic review conducted independently by the academic group were generally consistent with the results from the manufacturer and concluded that all articles important for the assessment of additional benefits were included. In contrast, the RCTs conducted under the Omicron variant/vaccination did not show any data to support the efficacy of ensitrelvir in preventing severe outcomes, improving symptoms, or suppressing post-COVID-19 conditions compared with the SoC. Therefore, the academic group concluded that in neither population (a) nor (b) did ensitrelvir demonstrate any additional benefit over the comparator, and that a cost minimization analysis was warranted.

Additionally, the academic group judged that the additional benefits of ensitrelvir were not proven in both populations (a) and (b) even when they referred to the data on other outcomes such as the time to resolution of the five COVID-19 symptoms, post-COVID-19 condition, and viral RNA levels given the following reasons: 1) The use of a combination cold remedy was prohibited in the T1221 trial. 2) "the time to resolution of the five COVID-19 symptoms" was defined as the time to resolution of all five COVID-19 symptoms. Cough and stuffy or runny nose were the most common endpoints, while feeling hot or feverish contributed minimally to the endpoints. 3) The clinical study protocol was repeatedly changed in the T1221 study. 4) The survey on post-COVID-19 conditions was conducted only on participants from the T1221 trial who provided separate consent to participate in the survey. Therefore, selection bias cannot be excluded from the

survey on post-COVID-19 conditions. 5) It was challenging to assess the clinical significance of changes in viral RNA levels.

5. Results of the cost-effectiveness analysis

The manufacturer performed a cost-effectiveness analysis using decision-tree and Markov models among population (a). In contrast, a cost-minimization analysis was performed among population (b). The academic group performed a cost-minimization analysis because ensitrelvir did not show any additional benefits over the SoC and nirmatrelvir/ritonavir. The ECCEE accepted the following results:

Population	Comparator	Additional benefit	ICER (JPY/QALY)
(a) Without risk factors for severe outcomes	SoC	Not proven	Cost increase
(b) With risk factors for severe outcomes	Nirmatrelvir/ritonavir	Not proven*	Cost increase

*The academic group performed a cost-minimization analysis on the condition that nirmatrelvir/ritonavir do not demonstrate any additional benefit over the SoC. If nirmatrelvir/ritonavir demonstrate any additional benefit over the SoC, the academic group will not perform a cost-minimization analysis, as they consider ensitrelvir to have inferior outcomes compared to nirmatrelvir/ritonavir.