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April 21, 2021

[C2H1903] Summary of cost-effectiveness evaluation of Ravulizumab (Ultomiris)

1. Indications

Paroxysmal nocturnal hemoglobinuria (PNH)

2. Drug price

Ravulizumab was reimbursed in September 2019 for JPY 730,894 (as of April 2021). The price was calculated using the similar efficacy comparison method, with a usefulness premium of 5%. This product is designated as an H1 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

Ravulizumab has indication for PNH. Standard therapy, eculizumab (Soliris), needs to be administered every 2 weeks, but ravulizumab is administered every 8 weeks. The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described hereafter. Eculizumab, which is the current standard therapy, was used as a comparator. On the contrary, best supportive care (BSC) could be a comparator for patients who were potentially targeted to eculizumab but did not receive it. However, the number of such patients is limited and it is possible that the results of the analysis have large uncertainties. Therefore, eculizumab was used as a comparator for the sensitivity analysis.

Population	Paroxysmal nocturnal hemoglobinuria (PNH)
Comparator	Eculizumab In addition, analysis of best supportive care (BSC) used as the comparator is performed as a sensitivity analysis.

4. Evaluation of additional benefits

Based on the systematic review, two randomized control trials (RCTs), the 301 and 302 trials, corresponding to the research questions were detected. In the 301 trial, patients with PNH treated with a complement inhibitor were selected. In contrast, the 302 trials included patients with PNH who received eculizumab for more than 6 months.

The manufacturer insisted that ravulizumab has an additional benefit to eculizumab in terms of "reduction of free C5-related breakthrough hemolysis (BTH)," "avoidance of blood transfusion," and "improvement in quality of life (QOL) because frequency of injection is reduced."

【Free C5-related BTH】

· According to the 301 and 302 trials, the incidence rate of free C5-related BTH was not significantly different between the groups.

· As the measurement of free C5 is not commonly used in clinical practice, the appropriateness of the endpoint was not clear.

· The dose of ravulizumab is determined based on the patient's weight. In contrast, eculizumab dosage is fixed regardless of the patient's body weight. Therefore, it is possible that the dose of eculizumab for patients with a high body weight was inadequate, thereby causing free C5-related BTH.

Avoidance of blood transfusions

According to the 301 and 302 trials, avoidance of blood transfusion was not significantly different between the groups.

【Improvement in QOL because the frequency of injections is reduced】

· The discrete choice experiment (DCE) was used to investigate preference in general people and not in patients. Such results cannot be used for the evaluation of additional benefits.

The academic group concluded that ravulizumab did not have an additional benefit to eculizumab. The third session of the ECCEE accepted the academic group's view.

5. Result of cost-effectiveness analysis

The manufacturer performed a cost-effectiveness analysis. However, as the additional benefit was not proven, the academic group performed a cost-minimization analysis. The comparative costing for 8 weeks showed that the cost of ravulizumab treatment was higher than that of eculizumab by JPY 343,163.

When BSC was used as a comparator, the academic group accepted the results submitted by the manufacturer, although the manufacture's submission had some problems.

Comparator	ICER (JPY/QALY)
eculizumab	Cost increase
BSC	101,700,385