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[C2H2202] Summary of cost-effectiveness evaluation of clazosentan (Pivlaz®)

1. Indication

Prevention of cerebral vasospasm, vasospasm-related cerebral infarction (CI), and cerebral ischemic symptoms after aneurysmal subarachnoid hemorrhage (aSAH) securing.

2. Price of the drug

Clazosentan has been reimbursed since April 2022 at JPY 80,596 (as of September 2023). The price was calculated based on the cost-calculation method. This product was designated as an H1 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described below. This product is used to prevent cerebral vasospasm, vasospasm-related CI, and cerebral ischemic symptoms after aSAH securing.

Population	Patients with aSAH securing
Comparator	Postoperative intensive care and management

4. Evaluation of additional benefits

The manufacturer performed a systematic review of randomized controlled trials (RCTs) and identified seven trials reported in six papers. Of these, they used AC-054-305 and AC-054-306 trials, which are RCTs including only Japanese patients, for evaluating additional benefits for the following reasons: both RCTs are the

prime confirmatory trials used to deduce the efficacy and safety of clazosentan during the regulatory approval in Japan; they judged that both RCTs were more reliable than others as a result of the quality evaluation; and the merged analysis of both RCTs is suited for the scope of cost-effectiveness evaluation because each RCT included patients secured by clipping and coiling, respectively. The manufacturer used (i) the incidence proportion of vasospasm-related delayed ischemic neurological dropout (DIND) and CI, and death from any reason within six weeks after aSAH securing; (ii) the incidence proportion of DIND, CI, and death from any reason within six weeks after aSAH securing; and (iii) the proportions of mRS 0-2* (mild), mRS 3-5 (severe), and mRS 6 (death) as the evaluation items. Clazosentan showed statistically significant efficacy for these items; thereafter, the manufacturer insisted on the additional benefits of clazosentan over the comparator. Based on the mRS, the academic group examined the availability of other trials identified in the systematic review but not used for evaluating additional benefits. Subsequently, the academic group clarified that the distribution of mRS differed between trials that included Japanese individuals and those that did not. This difference is probably due to trial design and population. Therefore, the academic group judged that an evaluation based on trials, including the Japanese patients, was appropriate. Additionally, although the academic group considered the availability of the AC-054-202 trial—an RCT including Japanese and Korean patients—there were concerns; for example, the trial set the dose differed from the dose approved in regulatory. Afterwards, the academic group judged that the manufacturer's method for evaluating additional benefits of clazosentan based on the AC-054-305 and AC-054-306 trials was appropriate. Furthermore, the academic group confirmed that clazosentan was still superior to the comparator, although this tendency was reduced when referring to the results of the merged analysis of AC-054-305, AC-054-306, and AC-054-202 (Japanese only).

*mRS(modified Rankin Scale): Seven levels of 0-6 indicating the degree of disability in the subject's daily activities (0 = no symptoms and 6 = death).

5. Results of the cost-effectiveness analysis

The manufacturer performed a cost-effectiveness analysis using a decision tree model expressing the acute phase of aSAH (initial six months) and a Markov model expressing the chronic phase of aSAH (after six months). The decision tree model was used to determine the distribution of mRS by defining death from any

reason as mRS 6, the incidence of vasospasm-related DIND and CI as mRS 3-5, and others as mRS 0-2. The academic group judged that the manufacturer's setting was not appropriate for the following reasons: other reasons excluding vasospasm also caused DIND and CI; the incidence of DIND and CI did not necessarily correspond to mRS 3-5; and the distribution of mRS itself was measured in the AC-054-305 and AC-054-306 trials. The academic group revised the distribution of the mRS, and a scenario analysis considering the AC-054-202 trial was performed. The ECCEE accepted the following results.

- Base-case

Population	Comparator	ICER (JPY/QALY)
Patients with aSAH securing	Postoperative intensive care and management	2,886,110

- Scenario analysis considering the AC-054-202 trial

Population	Comparator	ICER (JPY/QALY)
Patients with aSAH securing	Postoperative intensive care and management	4,195,896