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[C2H2207] Summary of cost-effectiveness evaluation of andexanet alfa (Ondexxya®)

1. Indication

Patients treated with Factor Xa (FXa) inhibitors apixaban, rivaroxaban or edoxaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

2. Price of the drug

Andexanet alfa has been reimbursed since May 2022 at JPY 338,671 (as of October 2023). The price was calculated based on the cost-calculation method. This product was designated as an H2 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 reverse the anticoagulant effect of FXa inhibitors in patients experiencing a life-threatening or uncontrolled bleed. As the effectiveness of andexanet alfa is not likely homogeneous depending on the part of bleeding, the population was divided into patients with intracranial hemorrhage (ICH) and patients with severe gastrointestinal (GI) bleeding. Additionally, as the doses of andexanet alfa are set according to the type, dose, and passed time from the final administration of FXa inhibitors, the population was further divided into low-dose administration and high-dose administration groups.

Population	Following patients treated with FXa inhibitors when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding: (a) Patients with ICH administered low-dose† andexanet alfa (b) Patients with ICH administered high-dose‡ andexanet alfa (c) Patients with severe GI bleeding administered low-dose† andexanet alfa (d) Patients with severe GI bleeding administered high-dose‡ andexanet alfa †400-mg intravenous injection at a rate of 30 mg/min, followed by 480-mg intravenous injection at a rate of 4 mg/min for 2 hours ‡800-mg intravenous injection at a rate of 30 mg/min, followed by 960-mg intravenous injection at a rate of 8 mg/min for 2 hours
Comparator	(a)(b)(c)(d): Standard of Care (SoC)* *excluding uninsured care

4. Evaluation of additional benefits

The manufacturer performed a systematic review and confirmed that there were no randomized controlled trials and other clinical trials comparing andexanet alfa and SoC directly. Thus, they evaluated the additional benefits based on the 30-day mortality by performing unanchored matching–adjusted indirect comparison (MAIC), which used aggregated data of SoC from a previous clinical study and individual participant data from the ANNEXA-4 extension trial—a single-arm trial for andexanet alfa. For comparator data, the manufacturer used Cohen's report, which performed propensity score matching between individual participant data of SoC in the ORANGE study—an observational study performed in the United Kingdom—and individual participant data in the ANNEXA-4 trial, and compared the 30-day mortality between them. Andexanet alfa showed statistically significant efficacy for the 30-day mortality according to the MAIC; thereafter, the manufacturer insisted on the additional benefits of andexanet alfa over the comparator in all populations. The academic group compared the characteristic information and 30-day mortality of the andexanet alfa group reported in the ANNEXA-4 trial in Cohen's report, ANNEXA-4 extension trial before

applying the MAIC, and ANNEXA-4 extension trial after applying the MAIC to evaluate the appropriateness of the manufacturer's MAIC. The result showed that the characteristic information was consistent in these three reports, but the 30-day mortality in the ANNEXA-4 extension trial after applying the MAIC was not consistent with the mortality in others. Thus, the academic group judged that the manufacturer's MAIC was not appropriate, and to refer to the data shown in the table as it was more appropriate because of lower uncertainty. The third ECCEE session concluded that the results of the academic group were more appropriate. Based on the discussion, andexanet alfa was judged to have additional benefits for all populations. However, it should be noted that this conclusion is accompanied with high uncertainty as only single-arm trial data were available for andexanet alfa during this evaluation process. In particular, an ongoing randomized controlled trial (ANNEXA-I), which compares andexanet alfa and SoC in patients with ICH, will provide important information for more robust evaluation.

Population	Data source	30-day mortality		
		Andexanet alfa	SoC	Difference
ICH	Costa et al.[1)]	7.9%	19.6%	Odds ratio, 0.36 (95% CI: 0.13–0.98)
Severe GI bleeding	Cohen et al.[2)]	12.2%	25.0%	Risk ratio, 0.49 (95% CI: 0.21–1.16)

CI: confidence interval; GI: gastrointestinal; ICH: intracranial hemorrhage; SoC: standard of care.

1) Costa OS, et al. Crit Care. 2022;26(1):180.
2) Cohen AT, et al. J Am Coll Emerg Physicians Open. 2022;3(2):e12655.

5. Results of the cost-effectiveness analysis

The manufacturer performed a cost-effectiveness analysis using a decision-tree model expressing the acute phase of major bleeding (initial 30 days) and a Markov model expressing the chronic phase of major bleeding. The decision-tree model was used to determine the distribution of death within 30 days after bleeding, and the manufacturer used the results of the evaluation of additional benefits as the transition probability. The academic group judged that the evaluation of additional benefits should not be based on the results of MAIC but

rather on the results from previous observational studies. Thus, the academic group revised the data source for determining the distribution of death. The ECCEE accepted the following results.

Population	Comparator	ICER (JPY/QALY)
(a) Low dose･ICH	SoC	2,724,603
(b) High dose･ICH	SoC	4,634,260
(c) Low dose･severe GI bleeding	SoC	1,460,215
(d) High dose･severe GI bleeding	SoC	2,628,387

GI: gastrointestinal; ICER: incremental cost-effectiveness ratio; ICH: intracranial hemorrhage; SoC: standard of care; QALY: quality-adjusted life year.