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[C2H1906] Summary of cost-effectiveness evaluation of Ivabradine (Coralan)

1. Indications

Chronic heart failure with resting heart rate 75 and above at the time of initial administration

2. Price of drug

Ivabradine was reimbursed from November 2019 for JPY 82.9 (2.5 mg), JPY 145.4 (5 mg), and JPY 201.9 (7.5 mg) as of May 2021. The price was calculated using a similar efficacy comparison method, with a usefulness premium of 35%. This product was designated as an H2 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

This product is a hyperpolarization-activated cyclic nucleotide–gated (HCN) channel blocker and has indications for patients with chronic heart failure who receive standard drug therapy including β blockers. The first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) determined that the target population should be chronic heart failure patients receiving β blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs). As ivabradine is used as an add-on to the standard therapy, only standard therapy (placebo) was selected as a comparator.

Target population	Chronic heart failure patients receiving β blockers, ACE inhibitors or ARBs and MRAs. Their left ventricular ejection fraction is 35% and below, and resting heart rate is 75 and above
Comparator	Only standard therapy (placebo)

4. Evaluation of additional benefits

The manufacturer identified eight clinical trials which evaluated the efficacy and safety of ivabradine by systematic review (SR). Six trials were excluded because they were abstracts for academic conferences. Only the literature on the SHIFT trial and J-SHIFT trial was included. The academic group extended the SR search period and researched based on the manufacturer's submission. As a result, 23 publications were detected, of which 22 publications were based on the SHIFT trial and post-hoc analysis of the SHIFT trial, and one was related to the J-SHIFT trial. The analysis of the academic group was consistent with the manufacturer's submission.

According to the J-SHIFT trial, 66% (82/124) and 73% (90/123) of patients received 15 mg of ivabradine per day, 4 weeks and 6 weeks after randomization, respectively. In comparison, in the actual clinical setting, more than half of all patients received only 2.5 mg or 5 mg of ivabradine per day, as estimated by the National Claims Database. The dose was much lower than that of the clinical trial. Therefore, the academic group questioned whether the clinical trial data can be extrapolated to calculate effectiveness in the actual clinical setting.

Dose	Number of patients
2.5 mg	50
5 mg	341
7.5 mg	Less than 10
10 mg	186
12.5 mg	Less than 10
15 mg	43
20 mg	Less than 10

The SHIFT trial and J-SHIFT trial showed that ivabradine reduced the risk of cardiac death. However, further consideration of the applicability of the clinical trial is needed if the actual dose is significantly different from the dose administered in the clinical trial. After the completion of this evaluation, monitoring of the dose should be continued and the product should be reevaluated if necessary.

5. Result of cost-effectiveness analysis

The manufacturer estimated cost-effectiveness using the Markov model. The academic group insisted that this analysis should be revised based on the following comments. The third session of the ECCEE agreed with the academic group.

· The manufacturer used 59.59 as the age of the target population based on the SHIFT trial. However, it is possible that patients enrolled in the clinical trial were younger than actual patients. The academic group estimated the actual age to be 68.76 through the National Claims Database. Therefore, this age was used for the cost-effectiveness analysis.

· The manufacturer assumes that the administration of ivabradine improves quality of life (QOL) even if it does not recover cardiac function. As this is not clinically supported, it is possible that this assumption leads to an overestimation of cost-effectiveness. Therefore, this effect should be regarded as zero, and cost-effectiveness recalculated based on this setting.

The result of the cost-effectiveness analysis reflecting these comments from the academic group is shown below.

Comparator	ICER (JPY/QALY)
Only standard therapy (placebo)	3,568,905

However, if the dose of ivabradine is significantly different between clinical trials and the actual clinical setting, and it raises questions about the applicability of the clinical trial data, the above ICER is not guaranteed.