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[C2H2304] Summary of cost-effectiveness evaluation of tenapanor (Phozevel®)

1. Indication

Improvement of hyperphosphatemia in patients with chronic kidney disease on dialysis

2. Price of the drug

Tenapanor has been reimbursed since November 2023 at JPY 234.1 for 5-mg tablets, JPY 345.8 for 10-mg tablets, JPY 510.9 for 20-mg tablets, and JPY 641.8 for 30-mg tablets (as of May 2025). The price was calculated based on the similar efficacy comparison method, with a usefulness premium of 40%. This product is 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 improve hyperphosphatemia in patients with chronic kidney disease on dialysis.

Population	(a) Treatment naïve or previously treated and controllable patients with hyperphosphatemia on dialysis (b) Previously treated and uncontrollable patients with hyperphosphatemia on dialysis
Comparator	(a) The less expensive of ferric citrate and sucroferric oxyhydroxide (b) Existing phosphorus binder

4. Evaluation of additional benefits

The manufacturer evaluated the additional benefits in population (a) based on pill-burden (number of pills) and (b) based on the changes in serum phosphorus level. For population (a), they cannot identify any randomized controlled trials (RCTs) that compared tenapanor and iron-containing phosphorus binder and referred to a single-arm trial of tenapanor (7791-007 trial). This trial evaluated the effectiveness of tenapanor by replacing other existing phosphorus binders with tenapanor in patients taking an average of 12 pills of phosphorus binders per day at the start of the trial. The patients at the end of the trial took 6 pills on average of agents for hyperphosphatemia including tenapanor. The manufacturer insisted on the additional benefits of tenapanor over ferric citrate, which was selected as a comparator owing to its lower costs, by extrapolating the results of 7791-007 trial: they judged that tenapanor can lower pill burden compared to ferric citrate by considering the numbers of pills at the start of the 7791-007 trial as the maintenance pills of ferric citrate; this is because these numbers were similar to those of maintenance pills in the long-term Phase III trial for ferric citrate. For population (b), the manufacturer identified an RCT comparing tenapanor and placebo in patients under uncontrollable hyperphosphatemia (7791-005 trial). This trial showed that the difference of changes in serum phosphorus level between tenapanor and placebo was -1.76 mg/dL (95% confidence interval：-2.16 to -1.37). Based on the result, they insisted on the additional benefits of tenapanor.

The academic group requested the manufacturer’s opinion about the serum phosphorus level in population (a). They submitted the results of matching-adjusted indirect comparison between tenapanor, ferric citrate, and sucroferric oxyhydroxide, showing the superior tendency of tenapanor over the other two. The academic group reviewed the appropriateness of the indirect comparison by referring to the results of 7791-004 trial for tenapanor because patient characteristics were similar between the trials of ferric citrate and sucroferric oxyhydroxide and the 7791-004 trial. Finally, the academic group could not obtain evidence of the superior tendency of tenapanor over iron-containing phosphorus binders for serum phosphorus levels. The academic group also judged that the pill burden was not appropriate as an outcome; if it were, tenapanor should be compared with sucroferric oxyhydroxide because its pill burden is lower than that of ferric citrate. Thus, the academic group set the comparator as sucroferric oxyhydroxide to maintain the consistency of the

evaluation process in population (a). Subsequently, the academic group judged that tenapanor has not shown additional benefits over sucroferric oxyhydroxide because no data about pill burden could be referred to. For population (b), the academic group judged that tenapanor has shown additional benefits over existing phosphorus binders based on the manufacturer's explanation.

As discussed, the third ECCEE session concluded that the academic group's results were more appropriate. Based on the discussion, tenapanor was judged to have additional benefits for population (b) but not for population (a).

5. Results of the cost-effectiveness analysis

The manufacturer performed cost-effectiveness analysis by using an analytical model that combined the decision-tree model, which determined the distribution of serum phosphorus levels, and the Markov model, which expressed the transition to cardiovascular events and death. For population (a), they assumed that the distributions of serum phosphorus levels were equal between groups. The model produced incremental effectiveness by applying the QOL score, which changed depending on the number of pills taken. For population (b), the distributions of serum phosphorus levels were different between groups, and then, less cardiovascular events and deaths occurred in the tenapanor group. The academic group performed cost-minimization analysis because tenapanor has not shown additional benefits for population (a). For population (b), the academic group judged that the manufacturer's analysis was acceptable. The ECCEE accepted the following results. Additionally, the academic group performed a sensitivity analysis based on cost-effectiveness analysis for population (a) to deal with the uncertainty of pill burden. As a result, this sensitivity analysis showed that the ICER of tenapanor for sucroferric oxyhydroxide is highly likely to be more than 10 million JPY/QALY.

Population	Comparator	Additional benefits	ICER (JPY/QALY)
(a) Treatment naïve or previously treated and controllable patients with hyperphosphatemia on dialysis	sucroferric oxyhydroxide	Not proven	Cost increase
(b) Previously treated and uncontrollable patients with	Existing phosphorus	Proven	3,414,644

hyperphosphatemia on dialysis	binder		