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[C2H2210] Summary of cost-effectiveness evaluation of Tezepelumab (Tezspire®)

1. Indication

Severe or refractory asthma in whom symptoms cannot be controlled with existing treatments

2. Price of the drug

Tezepelumab has been reimbursed since November 2022 at JPY 176,253 for syringe formulation and 178,182 for pen formulation (as of June 2024). The prices are calculated based on 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

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 treat severe or refractory asthma in whom symptoms cannot be controlled with existing treatments with no phenotype or biomarker limitations. Dupilumab was selected for the comparator in population (a-1).

Population	Severe or refractory asthma in whom symptoms cannot be controlled with existing treatments (a) Type 2 asthma (eosinophil counts [EOS]≥150/μL or IgE sensitization positive) (a-1) Type 2 asthma (EOS≥150/μL and IgE sensitization negative)

	(a-2) Type 2 asthma (IgE sensitization positive) (b) Non-type 2 asthma (EOS<150/μL and IgE sensitization negative)
Comparator	(a-1) Existing biologics (mepolizumab, benralizumab, and dupilumab) with the lowest price (a-2) Omalizumab (b) Standard of Care (SoC)* *including beta-agonists and steroids

4. Evaluation of additional benefits

The manufacturer performed a systematic review for studies regarding tezepelumab and comparators in each population. Although no randomized controlled trials (RCTs) comparing tezepelumab and other biologics were identified, four RCTs comparing tezepelumab and placebo were identified. One of them was the NAVIGATOR trial, which is the Phase III trial for tezepelumab. Three network meta-analysis (NMA) comparing biologics indirectly were also identified. The manufacturer sorted the studies while considering the definition of each population and evaluated the additional benefits of tezepelumab based on annual asthma exacerbation rate (AAER). The results were as follows: population (a-1) the additional benefits were not proven because no studies meeting the definition of this population were identified: (a-2) the additional benefits were proven because a NMA, which was performed based on the way similar to the identified NMA by Menzies-Gow, et al., showed a superior tendency of tezepelumab (AAER ratio against omalizumab, 0.61 [95% credible interval: 0.24 to 1.16]; and (b) the additional benefits were proven based on the result of re-analyzing the NAVIGATOR trial while considering the definition of this population. The academic group judged that the results of the manufacturer's evaluation were generally acceptable, but the academic group referred data including a subgroup analysis for patients at EOS≥150/μL in the NMA by Menzies-Gow, et al. to examine the validity of the conclusion for population (a-1). Based on the NMA by Menzies-Gow, et al., the AAER ratio against dupilumab 300 mg was 0.91 (95% credible interval: 0.58 to 1.44), and the point estimate was close to 1.0. Therefore, the academic group judged that the additional benefits of tezepelumab were not proven in population (a-1) even when they referred the data which may be extrapolatable to this population. In addition, it should be noted that the differences in the effectiveness between biologics accompanied a large

uncertainty because the academic group recognized that the extent to the differences varied according to which indirect comparison methods were selected on their review process.

5. Results of the cost-effectiveness analysis

The manufacturer performed a cost-effectiveness analysis using a Markov model consisting of five health states, "well controlled", "poor controlled", "exacerbation from well control", "exacerbation from poor control", and "death". The manufacturer calibrated the transition probability to "death" to higher value because the mortality rate calculated by the model was lower than 8.0%/2 years, which was reported by an epidemiological study for patients with severe asthma in France. However, the academic group removed the calibration because the mortality rate from the French study was higher than that reported by epidemiological data in Japan and the inconsistency between the population in the model and in the French study. The ECCEE accepted the following results.

Population	Comparator	Additional benefits	ICER (JPY/QALY)
(a-1) Type 2 asthma (EOS≥150/μL and IgE sensitization negative)	Dupilumab	Not proven	Cost increase
(a-2) Type 2 asthma (IgE sensitization positive)	Omalizumab	Proven	41,602,810
(b) Non-type 2 asthma (EOS<150/μL and IgE sensitization negative)	Soc	Proven	16,959,488