Center for Outcomes Research and Economic Evaluation for Health (C2H), National Institute of Public Health (NIPH) | URL: http://c2h.niph.go.jp

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[C2H1901] Summary of cost-effectiveness evaluation of Fluticasone/Umeclidinium/Vilanterol (Trelegy Ellipta)

1. Indications

Chronic obstructive pulmonary disease (COPD) [chronic bronchitis and pulmonary emphysema]

2. Price of drug

Trelegy Ellipta 100 was reimbursed from May 2019 for JPY 4183.5 (14 doses) and JPY 8853.8 (30 doses) (as of March 2021). The price was calculated by a similar efficacy comparison method with a usefulness premium of 10%. This product was designated as a H1 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

This product is enabled to perform triple therapy (ICS/LAMA/LABA) of COPD by one dose, not two doses. The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described hereafter. The manufacturer insisted the evaluation should be based on the ITT population of the randomized IMPACT trial. ECCEE agreed that evaluation should be performed based on the IMPACT trial. However, background of patients enrolled in IMAPCT trial had variety in terms of prior treatment they received. Because of it, ECCEE thought it was difficult to interpret the results of ITT population of the IMPACT trial. Therefore ECCEE decided that evaluation was performed every sub-population as follows; ITT population was divided into population C to L by prior treatment and eosinophil count, which reflected allergic symptoms. The cut off value of eosinophil count was 100/μL. 150/μL was also used as a sensitivity analysis. In addition, ECCEE agreed that exacerbation of COPD should be used as the outcome when additional benefits of Fluticasone/Umeclidinium/Vilanterol (FF/UMEC/VI) was evaluated.

Target population				Comparator
Prior treatment	Detailed prior treatment	Eosinophil count		
		<100/μL	≥100/μL	
Triple therapy	MITT (Triple therapy by two doses)	A	B	MITT (Triple therapy by two doses)
		C	D	ICS/LABA
		E	F	LAMA/LABA
Double therapy	ICS/LABA	G	H	ICS/LABA
Double therapy(LAMA/LABA) or single therapy		I	J	LAMA/LABA
Single therapy	LAMA	K	L	ICS/LABA
Others		No evaluation		-

MITT: Multiple Inhaler Triple Therapy

ICS: Inhaled corticosteroid

LABA: Long-Acting Beta2-Agonist

LAMA: Long-Acting Muscarinic Antagonist

4. Evaluation of additional benefits

Two non-inferiority trials were detected (207608 trial and 207609 trial) for evaluation of population A and B. Regarding other populations, no randomized control trials were found except the IMPACT trial, the manufacturer submitted. From these data, the manufacturer interpreted FF/UMEC/VI has additional benefit to all the population except population A and B. However the academic technology assessment group submitted the following report. The views of the academic group was agreed at the third session of ECCEE.

・ Population A and B: 207608 trial and 207609 trial proved non inferiority of FF/UMEC/VI to MITT. FF/UMEC/VI does not have additional benefit to population A and B.

・ Population C and D: Population C and D patients of the IMPACT trial who received prior triple therapy were randomly allocated to the double therapy group, independently from clinical indication (random stepdown of LAMA). Because stepdown is not randomly selected in the actual clinical practice, the results of IMPACT trial could not be applied to our evaluation. On the other hand, stepdown of

LAMA is not generally performed in the clinical practice. Therefore there were no comparative trial data on stepdown of LAMA. Considering them, the views of academic group was "Unable to analyze".

・ Population E and F: Similarly with population C and D, population E and F patients of in the IMPACT trial who received prior triple therapy were randomly allocated to double therapy, independently from clinical indication (random stepdown of ICS). Because stepdown is not randomly selected in the actual clinical practice, the results of IMPACT trial could not be applied to our evaluation. On the other hand, according to the meta-analysis of clinical trials which evaluated stepdown of ICS (COSMIC trial, WISDOM trial, INSTEAD trial and SUNSET trial), it suggested that stepdown of ICS did not relate with the increasing risk of exacerbation. Therefore FF/UMEC/VI does not have additional benefit to population E and F.

・ Population G, H, J, K and L: Based on the subgroup analysis of the IMPACT trial, risk ratio of moderate or severe exacerbation was less than 1 (significant in some populations and not significant in others). These results were not changed by a sensitivity analysis, which used a cut off value of eosinophil count as 150/μL. Therefore FF/UMEC/VI have additional benefit to these populations

・ Population I: Subgroup analysis of the IMPACT trial indicated that the only population I's risk ratio of moderate or severe exacerbation exceeded 1, different from other populations. In addition, clinical implication was not clear to the patients with low eosinophil count, who received LAMA or LAMA/LABA without ICS based on the assessment of clinicians. This result was supported by a sensitivity analysis, which used a cut off value of eosinophil count as 150/μL. Therefore FF/UMEC/VI does not have additional benefit to population I.

5. Result of cost-effectiveness analysis

For population A and B, the manufacturer assumed the clinical effectiveness was the same and performed the cost minimization analysis. For population C-L, the manufacturer did cost-effective analysis using Galaxy COPD model. The model can estimate ICER by inputting the difference of FEV1 between two groups. It used some risk equations made by foreign epidemiological studies.

The academic group revised the economic model based on the following issues.

・ For populations to which FF/UMEC/VI does not have additional benefit, cost-minimization analysis was performed. On the other hand, For populations to which FF/UMEC/VI have additional benefit, cost-effectiveness analysis was performed.

・Parameters of Patients' background inputted to the Galaxy COPD model should be calculated from the data of Japanese population, not ITT population.
・Based on the estimation by the Galaxy COPD model, the mortality between two groups was different. However post-hoc analysis of the IMPACT trial suggested no difference of the mortality. Model setting was changed so that the no difference of mortality was observed.

The academic group re-calculated the results. The results were submitted to the third session of the ECCEE and were approved. The final results obtained for each population are provided hereafter.

Population	Prior treatment	eosinophil count	Comparator	Additional benefit	ICER (JPY/QALY)
A	MITT (Triple therapy by two doses)	<100/μL	MITT (Triple therapy by two doses)	Not shown	Cost saving
B		≥100/μL		Not shown	Cost saving
C		<100/μL	ICS/LABA	"Unable to analyze"	
D		≥100/μL		"Unable to analyze"	
E		<100/μL	LAMA/LABA	Not shown	Cost increasing
F		≥100/μL		Not shown	Cost increasing
G	ICS/LABA	<100/μL	ICS/LABA	Yes	1,833,684
H		≥100/μL		Yes	328,585
I	LAMA/LABA or LAMA	<100/μL	LAMA/LABA	Not shown	Cost increasing
J		≥100/μL		Yes	Dominant
K	LAMA	<100/μL	ICS/LABA	Yes	Dominant
L		≥100/μL		Yes	483,056

USD 1 = JPY 105, and EUR 1=JPY 126 (as of March 2021)