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[C2H1905] Summary of cost-effectiveness evaluation of Vortioxetine (Trintellix)

1. Indications

Depression and depressive symptoms

2. Price of drug

Vortioxetine was reimbursed from November 2019 onward for JPY 168.90 (10 mg) and JPY 253.40 (20 mg) as of May 2021. The price was calculated using a similar efficacy comparison method, with a usefulness premium of 5%. This product was designated as an H1 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

This product is a serotonin reuptake inhibitor/serotonin receptor agonist and antagonist that has indications for depression and depressive symptoms. The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described hereafter. The target population was divided into (a) mild depression and depressive symptoms and (b) moderate and severe depression and depressive symptoms. According to clinical guidelines, antidepressants are not recommended as the main therapy for patients with mild depression. In contrast, new antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) are used for moderate or severe cases as the first choice in terms of efficacy and tolerability. However, superiority or inferiority were not shown among these new antidepressants. Therefore, (a) watchful waiting and (b) new antidepressants (SSRIs, SNRIs, and NaSSAs) with the lowest price were selected as a comparator for each population.

Target population	(a) Mild depression and depressive symptoms (b) Moderate and severe depression and depressive symptoms
Comparator	Population (a): Watchful waiting Population (b): New antidepressants (SSRIs, SNRIs, and NaSSAs) with the lowest price

4. Evaluation of additional benefits

To evaluate the additional benefits of vortioxetine for patients with mild illness, the manufacturer performed a systematic review (SR). However, no randomized controlled trials were identified. For patients with moderate or severe illness, the manufacturer revised a network meta-analysis by Cipriani et al. (2018) to Japanese clinical settings by limiting interventions to new antidepressants (SSRIs, SNRIs, and NaSSAs) approved by Japanese authorities. As the search period for SR was also extended, additional SR was performed. Data detected by SR were also included in the network meta-analysis. As a result, no difference in efficacy and tolerability was found between vortioxetine and other new antidepressants.

The academic group made inquiries to the manufacturer about an SR for patients with mild illness that includes all the new antidepressants. The results showed that no randomized controlled trials for any new antidepressants were identified.

The academic group approved these results.

5. Result of cost-effectiveness analysis

According to the manufacturer's submission, as no randomized controlled trials exist for patients with mild illness, cost-effectiveness is "impossible to analyze" for this population. The manufacturer submitted a cost-minimization analysis for patients with moderate or severe illness. Milnacipran was selected as a comparator because it is the cheapest among the new antidepressants. The manufacturer's analysis estimated treatment costs using the Markov model. However, the academic group insisted that the submitted Markov model has a high degree of uncertainty, for example, in terms of treatment duration. Therefore, the academic group compared the drug price per day assuming that efficacy and tolerability was equivalent. To compare the drug price, the academic group used the following prescription doses per day estimated by the National Claims Database.

	Generic name	Initial dose (mg)	Maximum dose (mg)	Average prescription dose per day (mg)
SSRI	Fluvoxamine	50	150	75.2
	Paroxetine	10-20 12.5 (CR)	40 50 (CR)	19.1
	Sertraline	25	100	49.8
	Escitalopram	10	20	11.9
SNRI	Milnacipran	25	100	50.1
	Duloxetine	20	60	35.1
	Venlafaxine	37.5	225	115.3
NaSSA	Mirtazapine	15	45	20.3
Others	Vortioxetine	10	20	13.5

The results of the cost-minimization analysis using the above estimation are shown below.

Target population	Comparator	ICER (JPY/QALY)
Mild	Watchful waiting	"Impossible to analyze"
Moderate and severe	Milnacipran	Cost increase

As a sensitivity analysis, an additional analysis that compared cost with all the new antidepressants was performed. Cost increased if fluvoxamine, paroxetine, sertraline, and mirtazapine were used as comparators. Cost of vortioxetine was lower compared with escitalopram, duloxetine, and venlafaxine.