Cost-effectiveness evaluation of Vortioxetine Hydrobromide (Trintellix)

(Academic Group)

[Version 1.0, March 25, 2021]
[Version 1.1, April 16, 2021]

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[Table of abbreviations]

Abbreviation	Formal description (English)
AE	Adverse event
ASMR	Amélioration du Service Médical Rendu
CADTH	Canadian Agency for Drugs and Technologies in Health
CENTRAL	Cochrane Central Register of Controlled Trials
CEA	Cost-Effectiveness analysis
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMA	Cost-Minimization Analysis
C-SSRS	Columbia-Suicide Severity Rating Scale
DESS	Discontinuation-Emergent Signs and Symptoms scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMBASE	Excerpta Medica Database
HAMD	Hamilton Depression Rating Scale
HAS	Haute Autorité de Santé
ICER	Incremental cost-effectiveness ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MEDLINE	Medical Literature Analysis and Retrieval System Online
NaSSA	Noradrenergic and specific serotonergic antidepressants
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
RCT	Randomized controlled trial
SAE	Serious adverse event
SMC	Scottish Medicines Consortium
SMR	Service Médical Rendu
SNRI	Serotonin noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor

0. Analytical framework

This analysis is for “Trintellix Tablets 10 or 20 mg (generic name, vortioxetine hydrobromide [hereinafter referred to as vortioxetine])”. The manufacturer is Takeda Pharmaceutical Company Limited. Vortioxetine is for the treatment of patients with depression or in a depressed state. It was selected as a subject of a cost-effectiveness evaluation in the general meeting of Central Social Insurance Medical Council (CSIMC) on November 13, 2019. Vortioxetine was expected to have a peak market size of 22.7 billion yen and fell under the H1 category of the cost-effectiveness evaluation (market size of ≥10 billion yen). The analytical framework for vortioxetine is shown in Table 0-1 approved by the Expert Committee of Cost-Effectiveness evaluation on March 19, 2020.

Table 0-1 Analytical framework

Population	(a) Patients with mild depression or in a mild depressed state[1] (b) Patients with moderate or severe depression or in a moderate or severe depressed state
Comparator	Population (a): no drug treatment [2] Population (b): the cheapest drug[4] of new generation antidepressants (SSRI, SNRI, and NaSSA)[3]
Reason for selecting the comparator	Population (a): According to the Clinical Practice Guidelines for Depression[5] in Japan, antidepressants are not recommended as a first-line treatment for patients with mild depression or in a mild depressed state and appropriate comparator is considered as no drug treatment. Population (b): According to the Clinical Practice Guidelines for Depression in Japan, antidepressant treatment is recommended for moderate or severe depression or moderate or severe depressed state. Among the antidepressants, new generation antidepressants, including SSRI, SNRI, or NaSSA, are used as a first-line treatment, though the superiority among these drugs has not been indicated.
Other perspective in addition to public healthcare payer	Yes (details:) ☒ No
Outcome and the reason if QALY is not used.	Not applicable
Other	The following sensitivity analyses are performed[6]: Population (a): scenario analysis with supportive psychotherapy or psychoeducation as a comparator Population (b): scenario analysis with each new generation antidepressant as a comparator

[1] In principle, “patients with depression or in a depressed state” refers to those with major depressive disorder as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) (hereinafter the same shall apply).
[2] “No drug treatment ” is defined as continuing consultation with a healthcare professional without any pharmacological interventions (hereinafter the same shall apply).
[3] New generation antidepressants are shown below (hereinafter the same shall apply):
SSRI (selective serotonin reuptake inhibitor): fluvoxamine, paroxetine, sertraline, and escitalopram

SNRI (serotonin noradrenaline reuptake inhibitor): milnacipran, duloxetine, and venlafaxine

NaSSA (noradrenergic and specific serotonergic antidepressant): mirtazapine

[4] Drugs and dosing regimens falling under the category of “the cheapest drug” will be discussed with the National Institute of Public Health (hereinafter the same shall apply).

[5] Clinical Practice Guidelines for Depression (2016) supervised by the Japanese Society of Mood Disorders (hereinafter the same shall apply)

[6] Details of the sensitivity analysis will be discussed with the National Institute of Public Health.

1.Summary of other HTA agency reviews

1.1 Overall summary

The manufacturer reported the summary of evaluations of vortioxetine by HTA agencies in the U.K., France, Germany, Canada, Australia, Ireland, Finland, Sweden, Korea, and Taiwan. The academic group investigated HTA evaluations in the U.K., France, Germany, Canada, and Australia, and compared the results. (Tables 1-1,1-2)

Table 1-1 HTA evaluations in other countries

Country	Agency	Evaluation result	
		Manufacturer	Academic group
U.K.	NICE	Recommended for treating adult MDD patients who failed to respond to 2 antidepressants	Recommended as a third-line treatment for MDD [November 2015] (1)
	SMC	Recommended for MDD patients who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/intolerability to two or more previous antidepressants)	Recommended as a third-line treatment for MDD [June 2016] (2)
France	HAS	SMR: moderate ASMR: V (No additional benefit) Efficiency evaluation: not performed	SMR: moderate ASMR: V (No additional benefit) [June 2015] (3)
Germany	IQWiG	Mild MDD: No additional benefit Moderate MDD: No additional benefit Severe MDD: No additional benefit	Mild MDD: No additional benefit Moderate MDD: No additional benefit Severe MDD: No additional benefit [April 2015] (4)
Canada	CADTH	Recommended (It should be reimbursed in a similar manner to other antidepressants, and the drug plan cost of treatment with vortioxetine should not	Recommended on the following conditions: • Reimburse in a similar manner to other antidepressants

		exceed the drug plan cost of the antidepressant currently reimbursed.)	• The drug plan cost of treatment with vortioxetine should not exceed the drug plan cost of the least costly antidepressant currently reimbursed. [April 2020] (5)
Australia	PBAC	Not recommended	Not recommended (rejected) [July 2014] (6)

Table 1-2 Implementation of cost-effectiveness evaluation in each agency

Country	Agency name	Manufacturer	Academic group
U.K.	NICE	✓	✓
	SMC	✓	✓
France	HAS	✓	X
Germany	IQWiG	✓	X
Canada	CADTH	✓	✓
Australia	PBAC	✓	✓(CMA)

Table 1-3 Result of cost-effectiveness evaluation in the U.K. (NICE)

Country	U.K.	
Agency name	NICE	
Reported by	Manufacturer	Academic group
URL	https://www.nice.org.uk/guidance/ta367	https://www.nice.org.uk/guidance/ta367
Result	Recommended for treating adult MDD patients who failed to respond to 2 antidepressants	Recommended as a third-line treatment for MDD
For a conditional recommendation, details of the conditions	Not applicable	Not applicable
Indication	Treatment of MDD episodes in adults (licensed indication)	Treatment of MDD in adults
Usage	The recommended and starting dose of Brintellix is 10 mg (as vortioxetine) once daily in adult patients <65 years. Depending on how the patients respond, the dose may be increased to a maximum of 20 mg once daily or decreased to a minimum of 5 mg once daily. Treatment for at least 6 months is recommended after the depressive symptoms resolve.	The recommended starting dosage is 10 mg once daily in adults <65 years, and 5 mg once daily in adults 65 years and older. Depending on how the symptoms respond, the dose may be increased to a maximum of 20 mg once daily or decreased to a minimum of 5 mg once daily. Treatment for at least 6 months is recommended after the symptoms resolve.
Comparator	Three SSRIs, two SNRIs, and agomelatine	Direct comparison: agomelatine and escitalopram Indirect comparison: agomelatine, citalopram, sertraline, venlafaxine, bupropion, and duloxetine
Main incremental cost-	Reviewer's results: ICER≤£9,000/QALY	**ICERs reported by the manufacturer:** £378/QALY

effectiveness ratio (ICER)		compared with venlafaxine as a second-line treatment **ICERs reported by the reviewer:** £9,000/QALY (compared with other antidepressants)

Table 1-4 Result of cost-effectiveness evaluation in the U.K. (SMC)

Country	U.K.	
Agency name	SMC	
Reported by	Manufacturer	Academic group
URL	https://www.scottishmedicines.org.uk/media/2492/vortioxetine_brintellix_final_june_2016_for_website.pdf	https://www.scottishmedicines.org.uk/media/2492/vortioxetine_brintellix_final_june_2016_for_website.pdf
Result	Recommended for MDD patients who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/intolerability to two or more previous antidepressants)	Conditional recommendation (SMC restriction)
For a conditional recommendation, details of the conditions	Not applicable	Third-line treatment for MDD
Indication	Treatment of major depressive episodes in adults	Treatment of MDD in adults
Usage	The recommended and starting dose of Brintellix is 10 mg (as vortioxetine) once daily in adult patients <65 years. Depending on how the patients respond, the dose may be increased to a maximum of 20	In adults <65 years, 10 mg taken once daily. The dose may be increased to a maximum of 20 mg once daily or decreased to a minimum of 5 mg once daily. In adults ≥65 years, 5 mg taken once daily.

	mg once daily or decreased to a minimum of 5 mg once daily. Treatment for at least 6 months is recommended after the depressive symptoms resolve.	After the depressive symptoms resolve, treatment for at least 6 months is recommended.
Comparator	Venlafaxine, mirtazapine, and duloxetine	Venlafaxine, venlafaxine IR, venlafaxine XR, sertraline, and agomelatine
Main incremental cost-effectiveness ratio (ICER)	Reviewer's results: Despite the uncertainty of the comparison, the economic base has been demonstrated.	**ICERs reported by the manufacturer:** ・ £1,997/QALY compared with venlafaxine IR ・ £1,351/QALY compared with venlafaxine XR ・ £2,868/QALY compared with sertraline ・ dominated by agomelatine **Reviewer's results:** Cost-effectiveness conclusions were found to vary according to the analysis conditions.

Table 1-5 Result of cost-effectiveness evaluation in Canada

Country	Canada	
Agency name	CADTH	
Reported by	Manufacturer	Academic group
URL	https://www.cadth.ca/vortioxetine-hydrobromide	https://www.cadth.ca/vortioxetine-hydrobromide
Result	Recommended (It should be reimbursed in a similar manner to other antidepressants, and the drug plan cost of treatment with vortioxetine should not exceed the drug plan cost of the antidepressant currently reimbursed.)	Conditional recommendation
For a conditional recommendation, details of the conditions	Not applicable	・Reimburse in a similar manner to other antidepressants ・The drug plan cost of treatment with vortioxetine should not exceed the drug plan cost of the least costly antidepressant currently reimbursed.
Indication	Treatment of adult patients with MDD	Treatment of adult patients with MDD
Usage	The starting and recommended dose is 10 mg (as vortioxetine) once daily in adults <65 years. Depending on individual patient response and tolerability, the dose may be increased to a maximum of 20 mg once daily. A dose decrease to a minimum of 5 mg once daily may be considered for patients who do not tolerate higher doses.	The starting and recommended dosage is 10 mg (as vortioxetine) once daily for adults <65 years. Depending on individual patient response and tolerability, the dosage may be increased to a maximum of 20 mg once daily. A dosage decrease to a minimum of 5 mg once daily may be considered for patients who do not tolerate higher doses.

		The recommended starting dosage for patients ≥65 years is 5 mg once daily.
Comparator	SNRI, SSRI, bupropion, and mirtazapine	Duloxetine, venlafaxine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, and mirtazapine
Main incremental cost-effectiveness ratio (ICER)	Reviewer's results: The difference in QALYs between vortioxetine and all comparators was minimal, suggesting a similar overall treatment benefit for patients with MDD.	**ICER reported by the manufacturer:** CAD 89,785/QALY compared with duloxetine **Reviewer's results:** ・ dominated by escitalopram and duloxetine ・ CAD 92,364/QALY compared with bupropion (scenario analysis) ・ The difference in QALYs between vortioxetine and all comparators is minimal, suggesting a similar overall treatment benefit for patients with MDD.

1.2 Critique on manufacturer's review

The review results of HTA agencies in foreign countries summarized by the manufacture was consistent with the academic group, except for the following:

1. There was a discrepancy in the interpretation of the evaluation result between SMC and CADTH (i.e., "Recommendation" or "Conditional recommendation").
2. As for the implementation of cost-effectiveness evaluations in each agency, the manufacturer reported that all assessment agencies had "performed cost-effectiveness evaluations." In contrast, the review of the academic group indicated that cost-effectiveness evaluations had been performed in the U.K. and Canada, but not been performed in any other countries.
3. The manufacturer reported that the main ICER for NICE was "below £9,000/QALY (Appraisal Committee)." On the other hand, according to the review of the academic group, the manufacturer first reported that the ICER for vortioxetine compared with venlafaxine as a second-line treatment was £378/QALY and, based on the result of re-analysis, the ICER for vortioxetine compared with antidepressants, excluding SSRIs, as a third-line treatment was shown as ≤£9,000/QALY.
4. The manufacturer reported as the reviewer's results that, despite the uncertainty of the comparison, the economic case had been demonstrated for the main ICER for SMC. On the other hand, according to the review of the academic group, the manufacturer reported that the ICERs for vortioxetine versus venlafaxine IR and XR and sertraline were £1,997, £1,351, and £2,868 per QALY, respectively, and vortioxetine was dominated by agomelatine. The result of the re-analysis suggested that the cost-effectiveness conclusions of vortioxetine would vary according to analysis conditions.
5. The manufacturer reported that the evaluation result of CADTH was "recommended" (it should be reimbursed in a similar manner to other antidepressants, and the drug plan cost of treatment with vortioxetine should not exceed the drug plan cost of the antidepressant currently reimbursed). When reviewed by the academic group, the evaluation result was "conditional recommendation," and the following conditions were imposed:
    - Reimburse in a similar manner to other antidepressants for the treatment of patients with MDD.
    - The drug plan cost of treatment with vortioxetine should not exceed the drug plan cost of the least costly antidepressant currently reimbursed.
6. As for the main ICERs for CADTH, the manufacturer reported that the difference in QALYs between vortioxetine and all comparators was minimal, suggesting a similar

overall treatment benefit for patients with MDD. On the other hand, according to the review of the academic group, the base case analysis of CADTH showed that vortioxetine was dominated by escitalopram and duloxetine (i.e., associated with greater costs and fewer QALYs), and the scenario analysis revealed that the ICER for vortioxetine compared with bupropion was CAD 92,364 per QALY. However, it was pointed out that the difference in QALYs between vortioxetine and all comparators was minimal, suggesting a similar overall treatment benefit for patients with MDD.

2. Evaluation of additional benefit

2.1. Systematic review by academic group

2.1.1 Research question

To examine the additional benefit of vortioxetine, a systematic review was performed based on the research questions as presented in Table 2-1. The populations were set as (a) patients with mild depression or in a mild depressed state and (b) patients with moderate or severe depression or in a moderate or severe depressed state, the intervention as vortioxetine, and the comparators as (a) no drug treatment for patients with mild depression or in a mild depressed state and (b) new generation anti-depressants for patients with moderate or severe depression or in a moderate or severe depressed state. The outcomes were efficacy such as improvement in depressed state and safety. For the study design, a systematic review of existing systematic reviews was performed as Step 1, and then a systematic review that intended to identify relevant randomized controlled studies published after the latest clinical studies identified in the previously reported systematic reviews was carried out as Step 2. The search period was from before the start of [redacted] of vortioxetine in Japan ([redacted]) to the date of the literature search in May 2020 for Step 1, and from after the period of the previously reported systematic reviews to the date of the literature search in May 2020 for Step 2.

Table 2-1 Research questions of the systematic review in the academic group

	Description
Population	(a) Patients with mild depression or in a mild depressed state (b) Patients with moderate or severe depression or in a moderate or severe depressed state
Intervention	Vortioxetine
Comparator	(a) No drug treatment for patients with mild depression or in a mild depressed state (b) New generation antidepressants for patients with moderate or severe depression or in a moderate or severe depressed state
Outcome	Improvement in depressed state, selected as the primary endpoint Safety
Study design	Two-step systematic review Step 1: Systematic review, meta-analysis, and network meta-analysis

	Step 2: Randomized controlled studies
Period of literature search	(1) [redacted] to May 2020 (2) After the period of the previously reported systematic reviews until May 2020

2.1.2 Flow of systematic review

2.1.2.1 Population (a) mild depression or in a mild depressed state

According to the Clinical Practice Guidelines for Depression published by the Japanese Society of Mood Disorders (7), DSM-5 is used to define mild depression as the individual must be experiencing five or more symptoms, most of the day, nearly every day, during the same 2-week period, and at least one of the symptoms should be either “depressed mood” or “loss of interest or pleasure”. The guideline also states that *“Some overseas guidelines propose using depression severity rating scales to define mild depression. Patients are given a diagnosis of a depressive state if they have a score of 8 to 13 on the Hamilton Depression Rating Scale, and a diagnosis of mild depression if they have a score of 14 to 18 in the NICE guidelines in the U.K. According to the APA guidelines in the U.S., patients are diagnosed with mild depression if they have a score of 8 to 13, and with moderate depression if they have a score of 14 to 18. As we observe in these guidelines, there is no consensus about the diagnosis of mild depression (p.29)*”. It was anticipated that exact screening of “patients with mild depression or in a mild depressed state” would have limitations as a strategy for literature search. Therefore, the population was set as “patients with depression or in a depressed state” in the search of evidence. Then, the patients included in the identified studies were screened afterwards to determine whether any patients in the studies met the criteria for mild depression defined as if they had a MADRS score of 19 or lower (8) (9) since the MADRS scores were most commonly used in the clinical studies for vortioxetine.

2.1.2.2 Population (b) patients with moderate or severe depression or in a moderate or severe depressed state

For the assessment of additional benefits of vortioxetine in patients with moderate or severe depression or in a moderate or severe depressed state, a two-step systematic review was performed with reference to the Minds Handbook for Clinical Practice Guideline Development (10) (Figure 2-1).

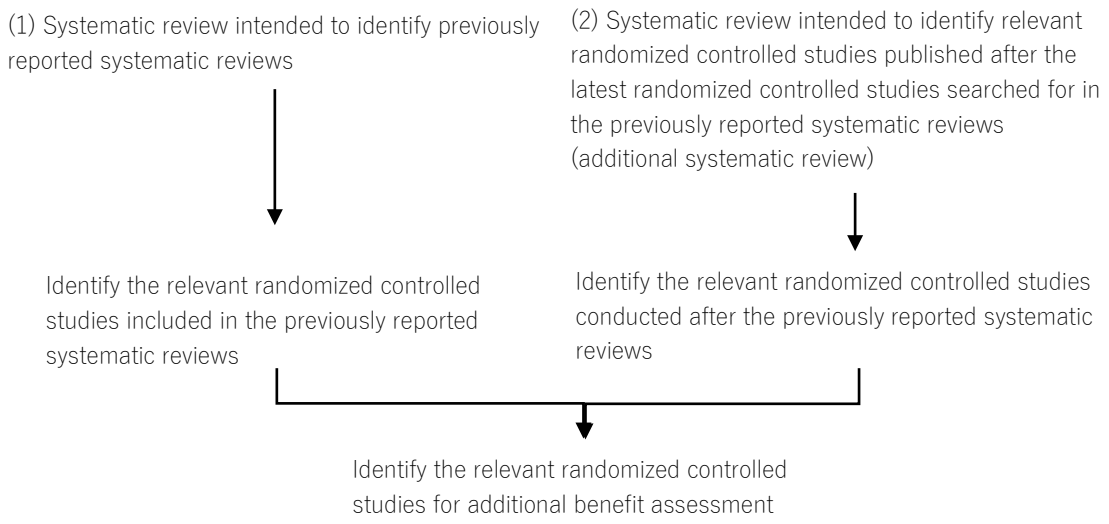

Figure 2-1 Flow of two-step systematic review

A medical information services/literature search expert developed the search strategy by combining conditions for disease name, drug name, study design, and search period. Screening based on literature abstracts was performed blinded by 2 independent reviewers. Inclusion or exclusion of literature was determined on the basis of the prespecified inclusion and exclusion criteria, and inconsistencies between the reviewers that occurred during the process were resolved through discussion by both reviewers.

2.1.3 Inclusion and exclusion criteria

<Inclusion criteria>

- Disease as depression or depressed state
- Intervention as vortioxetine
- Study design as systematic review in Step 1 and a randomized controlled study in Step 2
- Published during the designated period
- Written in English or Japanese

<Exclusion criteria>

Abstracts or meeting minutes

2.1.4 Databases

PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, and Ichushi-Web.

2.1.5 Search strategy

Search strategy for PubMed
Date of search: May 7, 2020
"Depressive Disorder"[MH] OR "Depression"[MH] OR "depressive"[TW] OR "depression"[TW]) AND ("Vortioxetine"[MH] OR vortioxetine[TIAB] OR brintellix[TIAB] OR "Lu AA21004"[TIAB]) AND (systematic[SB] OR "Network Meta-Analysis"[MH] OR "Meta-Analysis as Topic"[MH] OR "Randomized Controlled Trials as Topic"[MH] OR "Meta-Analysis"[PT] OR "meta analysis"[TI] OR "network meta analysis"[TI]) AND 2015:2020[PDAT]
A total of 51 publications

Search strategy for Embase
Date of search: May 7, 2020
(EMB.EXACT.EXPLODE("depression") AND EMB.EXACT("vortioxetine")) AND (EMB.EXACT.EXPLODE("systematic review") OR EMB.EXACT.EXPLODE("meta analysis") OR EMB.EXACT("network meta-analysis")) AND PD(2015-2020)
A total of 93 publications

Search strategy for Cochrane	
Date of search: May 7, 2020	
#1	(depressive):ti,ab,kw OR (depression):ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Depressive Disorder] explode all trees
#3	MeSH descriptor: [Depression] explode all trees
#4	(vortioxetine):ti,ab,kw OR (brintellix):ti,ab,kw OR (Lu AA21004):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Vortioxetine] explode all trees
#6	(#1 OR #2 OR #3) AND (#4 OR #5) in Cochrane Reviews
A total of 1 publication	

Search strategy for Ichushi
Date of search: May 7, 2020
うつ病/TH or 抑うつ/TH or 鬱/TA) and (Vortioxetine/TH or ボルチオキセチン/TA or トリンテリックス/TA or Vortioxetine/TH or brintellix/TA) and PT=原著論文 and DT=2015:2020
A total of 2 publications

The search strategy for the systematic review intended to identify relevant randomized controlled studies published after the latest randomized controlled studies identified in the previously reported systematic reviews are presented below:

Search strategy for PubMed
Date of search: May 7, 2020
"Depressive Disorder"[MH] OR "Depression"[MH] OR "depressive"[TW] OR "depression"[TW]) AND ("Vortioxetine"[MH] OR vortioxetine[TIAB] OR brintellix[TIAB] OR "Lu AA21004"[TIAB]) AND ("Randomized Controlled Trial"[PT] OR ("randomized"[TI] AND (trial[TI] OR trials[TI])) OR "double blind"[TIAB]) AND 2016:2020[PDAT]
A total of 54 publications

Search strategy for Embase
Date of search: May 7, 2020
EMB.EXACT.EXPLODE("depression") AND EMB.EXACT("vortioxetine") AND (EMB.EXACT.EXPLODE("randomized controlled trial")) AND PD(2016-2020)
A total of 55 publications

Search strategy for Cochrane	
Date of search: May 7, 2020	
#1	(depressive):ti,ab,kw OR (depression):ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Depressive Disorder] explode all trees
#3	MeSH descriptor: [Depression] explode all trees
#4	(vortioxetine):ti,ab,kw OR (brintellix):ti,ab,kw OR (Lu AA21004):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Vortioxetine] explode all trees
#6	(#1 OR #2 OR #3) AND (#4 OR #5) with Publication Year from 2016 to 2020, in Trials

A total of 85 publications

Search strategy for Ichushi
Date of search: May 7, 2020
うつ病/TH or 抑うつ/TH or 鬱/TA) and (Vortioxetine/TH or ボルチオキセチン/TA or トリンテリックス/TA or Vortioxetine/TA or brintellix/TA) and PT=原著論文 and DT=2016:2020
A total of 2 publications

2.1.6 Search results

The results of the systematic review are summarized as shown in Figure 2-2.

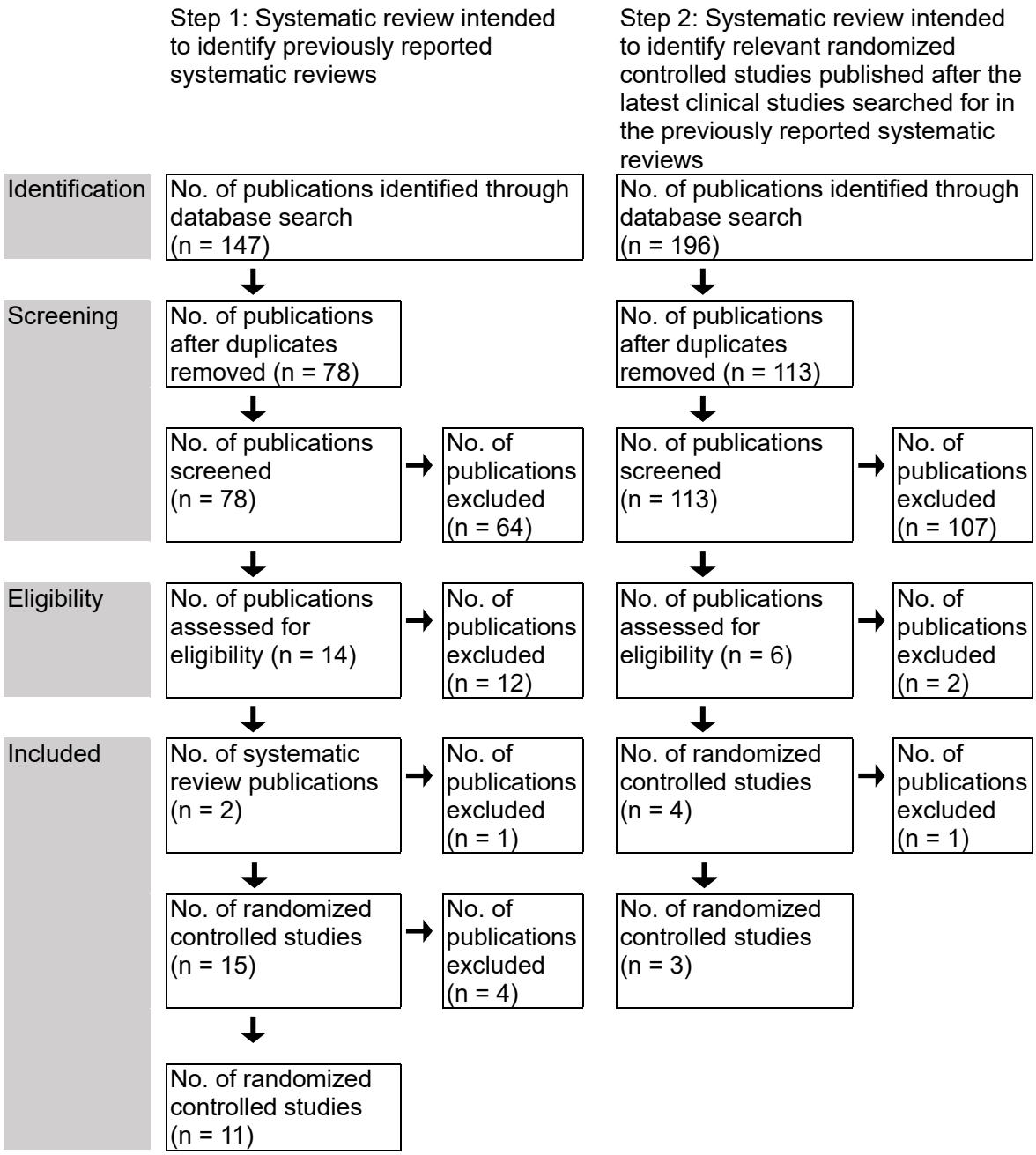

Figure 2-2 Summary of results of systematic review

The following two systematic reviews were identified:

1. Cipriani, Andrea, et al. "Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis." Lancet 16.4 (2018): 420-429.
2. Wagner, Gernot, et al. "Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: A systematic review and network meta-analysis." Journal of Affective Disorders 228 (2018): 1-12.

Table 2-2 Summary of the literature identified as previously reported systematic reviews

Literature	Cipriani et al. (2018) (11)	Wagner et al. (2018) (12)
No. of enrolled studies	522	24
No. of enrolled subjects	116,477	4,023
Duration of subject registration	From the start of collection of the database to January 8, 2016	From January 2010 to September 2017
Population	Patients with acute-phase MDD aged ≥18 years	Adult patients with MDD
Key exclusion criteria	Studies that included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness	Studies that enrolled patients aged ≥65 years
Study design	Double-blind RCTs	Double-blind RCTs for efficacy and non-randomized studies with a sample size of ≥100 for safety

Drugs	Second-generation antidepressants Agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone, vortioxetine), tricyclic antidepressants (amitriptyline, clomipramine), trazodone, and nefazodone (21 drugs in total)	Second-generation antidepressants Bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, vilazodone, vortioxetine, and trazodone
Bias assessment	The Cochrane Handbook for Systematic Reviews of Interventions, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework	Grades the strength of evidence with Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality
Primary endpoint	The efficacy outcome was response rate (proportion of patients who had a reduction of ≥50% of their total score on a standardized observer-rating scale for depression compared to baseline). The safety outcome was the proportion of patients who discontinued treatment due to any cause.	Response rate (a reduction of ≥50% of the HAM-D score compared to baseline)
Enrollment of patients with mild depression	No	No

The study by Wagner et al. (2018) enrolls adult patients with MDD and presents pooled results of 24 previous clinical studies (placebo- and active-controlled studies) with 16 different new generation antidepressants (including those not marketed in Japan) as comparators. This study was conducted to compare the efficacy and safety mainly on levomilnacipran, vilazodone, and vortioxetine with those of other new generation antidepressants; however, it was excluded from this review because levomilnacipran and vilazodone had not been approved in Japan .

The study by Cipriani et al. (2018) enrolls adult patients with MDD and presents pooled results of 522 previous clinical studies (placebo- and active-controlled studies) using 21 different antidepressants (including those not marketed in Japan) as comparators. This is the most comprehensive study of the efficacy and safety of new generation antidepressants, including vortioxetine, and it does not narrow the framework of the academic group.

For the studies of vortioxetine enrolled in the study by Cipriani et al. (2018), 15 placebo- and active-controlled studies were identified. Of the 15 studies, two studies conducted by McIntyre et al. (2014) (13) and Mahableshwarkar et al. (2015) (14) were excluded from this analysis because the primary outcome was improvement in cognitive function in both studies. Two studies (CCT002 involving Japanese subjects; CCT003 including Japanese subjects), which were not published at the time of publication of the research paper by Cipriani et al. (2018), were identified as previously reported RCT publications in the additional systematic review described later. A total of 11 studies listed below were identified as randomized controlled studies searched for in the previously reported systematic review. None of the studies enrolled patients with mild depression.

<List of the randomized controlled studies>

1. Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. International Journal of Neuropsychopharmacology. 2012;15(5):589-600.
2. Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). European Neuropsychopharmacology. 2012;22(7):482-91.

3. Boulenger J-P, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. International clinical psychopharmacology. 2014;29(3):138.
4. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. The Journal of clinical psychiatry. 2012;73(7):953-9.
5. Jacobsen PL, Mahableshwarkar AR, Serenko M, Chan S, Trivedi MH. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. The Journal of clinical psychiatry. 2015;76(5):575-82.
6. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. International Journal of Neuropsychopharmacology. 2013;16(2):313-21.
7. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. International clinical psychopharmacology. 2012;27(4):215-23.
8. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Current medical research and opinion. 2013;29(3):217-26.
9. Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. Psychopharmacology. 2015;232(12):2061-70.
10. Mahableshwarkar AR, Jacobsen PL, Serenko M, Chen Y, Trivedi MH. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. The Journal of clinical psychiatry. 2015;76(5):583-91.
11. Wang G, Gislum M, Filippov G, Montgomery S. Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study. Current medical research and opinion. 2015;31(4):785-94.

For Step 2, 4 studies, including 2 (CCT002 involving Japanese subjects; CCT003 including Japanese subjects) that were not published at the time of publication by Cipriani et al. (2018), were identified. Of them, the publication by Wang et al. (2019) (15) was excluded from this review due to its withdrawal after publication. The following 3 studies were identified as relevant randomized controlled studies:

1. Nishimura A, Aritomi Y, Sasai K, Kitagawa T, Mahableshwarkar AR. Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder. Psychiatry and Clinical Neurosciences. 2018;72(2):64-72.
2. Inoue T, Nishimura A, Sasai K, Kitagawa T. Randomized, 8-week, double-blind, placebo-controlled trial of vortioxetine in Japanese adults with major depressive disorder, followed by a 52-week open-label extension trial. Psychiatry and clinical neurosciences. 2018;72(2):103-15.
3. Inoue T, Sasai K, Kitagawa T, Nishimura A, Inada I. Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of vortioxetine in Japanese patients with major depressive disorder. Psychiatry and clinical neurosciences. 2020;74(2):140-8.

2.1.7 Summary of clinical studies

Table 2-3 Summary of the clinical studies included in the previously reported systematic reviews

ID	Literature No.	Study name/ year	Sample size	Drug name	Prescribed dose (mg)	Key eligibility criteria	Key exclusion criteria	Primary outcome
1	(16)	11492A, NCT00839423/2007	426	Placebo	-	MDD(DSM-IV-TR criteria), Current MDE≥3 mths and < 12mths, Age ≥18 and ≤65 years, MADRS total score ≥30	Current psychiatric disorder other than MDD, History of manic or hypomanic episode, schizophrenia, any other psychotic, mental or neurological disorder (other than MDD), Current substance abuse, Significant risk of suicide, attempted suicide in past 6 months, or score ≥5 on MADRS item 10 (suicidal thoughts), Treatment-resistant depression (defined as non-response to 2 antidepressant treatments of at least 6-week duration), History of lack of response to duloxetine (11984A, 13267A, 12541A, 304, 315) or venlafaxine (11492A, 13926A), Currently	Change from baseline to week 6 in MADRS
				Vortioxetine	5			
					10			
				Venlafaxine	225			
2	(17)	11984A, NCT00635219/2009	766	Placebo	-	MDD(DSM-IV-TR criteria), Current MDE≥ 3 mths, MADRS≥26, Age≥18 and ≤75 yrs old,		Change from baseline to week 8 in MADRS
				Vortioxetine	2.5			
					5			
					10			
				Duloxetine	60			
3	(18)	13267A, NCT01140906/2011	607	Placebo	-	Recurrent MDD(DSM-IV-TR criteria), Current MDE≥3 mths, MADRS≥26, CGI-S score ≥ 4, Age≥18 and ≤75 yrs old		
				Vortioxetine	15			
					20			
				Duloxetine	60			
				Vortioxetine	5			
				Duloxetine	60			
4	(19)	304, NCT00672620/2008	611	Placebo	-	MDD(DSM-IV-TR criteria), Current MDE≥3 mths, MADRS≥22, Age≥18 and ≤75 yrs old		Change from baseline to week 8 in HAM-D24
				Vortioxetine	2.5			
					5			
				Duloxetine	60			

5	(14)	315, NCT01153009/2012	614	Placebo	-	Recurrent MDD(DSM-IV-TR criteria), Current MDE≥3 mths, MADRS≥26, CGI-S score ≥ 4, Age≥18 and ≤75 yrs old	receiving cognitive or behavioral therapy or systematic psychiatry	Change from baseline to week 8 in MADRS
				Vortioxetine	15			
				Vortioxetine	20			
				Duloxetine	60			
6	(20)	NCT01571453, KCT0000432, 13926A/2013	437	Vortioxetine	10	Recurrent MDD(DSM-IV-TR criteria), Current MDE≥3 mths, MADRS≥26, CGI-S score ≥ 4, Age≥18 and ≤65 yrs old		
				Venlafaxine	150			
7	(21)	12541A, NCT00811252/2010	453	Placebo	-	MDD(DSM-IV-TR criteria), MADRS≥26, elderly ≥ 65yrs old, MDE ≥4 weeks in duration, At least 1 MDE before age of 60 years	Current psychiatric disorder other than MDD, History of manic or hypomanic episode, schizophrenia, any other psychotic, mental or neurological disorder (other than MDD), Current substance abuse, Significant risk of suicide, attempted suicide in past 6 months, or score ≥5 on MADRS item 10 (suicidal thoughts), Mini-Mental State Exam < 24	Change from baseline to week 8 in HAM-D24
				Vortioxetine	5			
				Duloxetine	60			
8	(22)	305, NCT00735709/2009	560	Placebo	-	MDD(DSM-IV-TR criteria), Current MDE≥3 mths, MADRS≥26, Age≥18 and ≤75 yrs old	Current psychiatric disorder other than MDD, History of manic or hypomanic episode. schizophrenia, Any other psychotic, mental or	Change from baseline to week 8 in HAM-D24
				Vortioxetine	1			
					5			
					10			

9	(23)	316, NCT01163266 /2012	462	Placebo	-	Recurrent MDD(DSM-IV-TR criteria), CGI-S score ≥ 4, MADRS≥26, Age≥18 and ≤75 yrs old	neurological disorder (other than MDD), Significant risk of suicide, attempted suicide in past 6 months, or score 5 on MADRS item 10 (suicidal thoughts), Treatment-resistant depression (defined as non-response to 2 antidepressant treatments of at least 6-week duration)	Change from baseline to week 8 in MADRS
				Vortioxetine	10			
				Vortioxetine	20			
10	(24)	303, NCT00672958 /2008	600	Placebo	-	MDD (DSM-IV-TR criteria), Current MDE≥3 mths, MADRS≥30, Age≥18 and ≤75 yrs old		Change from baseline to week 6 in HAM-D24 and at each week of treatment
				Vortioxetine	5			
11	(25)	317, NCT01179516/2012	469	Placebo	-	Recurrent MDD (DSM-IV-TR criteria), CGI-S score ≥ 4, Current MDE≥3 mths, MADRS≥26, Age≥18 and ≤75 yrs old		Change from baseline to week 8 in MADRS
				Vortioxetine	10			
				Vortioxetine	15			

Table 2-4 Efficacy outcomes (1) change in MADRS (2) change in HAM-D24 (the primary outcomes are shaded with)

ID	Study name/year	Drug name	Prescribed dose (mg)	(1) Change in MADRS			(2) Change in HAM-D24		
				Mean difference of placebo versus the comparator					
				Mean (SE)	95% CI	p-value	Mean (SE)	95% CI	p-value
1	11492A, NCT00839423/ 2007	Placebo	-	-	-	-			
		Vortioxetine	5	-5.90 (1.39)	-8.64 – -3.17	<0.001	-5.28 (1.22)	-7.69 – -2.88	<0.001
			10	-5.70 (1.42)	-8.49 – -2.91	<0.001	-5.33 (1.25)	-7.79 – -2.88	<0.001
		Venlafaxine	225	-6.42 (1.38)	-9.13 – -3.72	<0.001	-5.09 (1.21)	-7.48 – -2.70	<0.001
2	11984A, NCT00635219/ 2009	Placebo	-	-	-	-			
		Vortioxetine	2.5	-1.38 (1.12)	-3.59 – 0.82	0.22	-1.11 (1.12)	-3.31 – 1.10	0.32
			5	-1.70 (1.13)	-3.92 – 0.51	0.13	-1.79 (1.13)	-4.01 – 0.42	0.11
			10	-1.50 (1.13)	-3.73 – 0.72	0.18	-1.63 (1.13)	-3.85 – 0.59	0.15
		Duloxetine	60	-2.04 (1.14)	-4.27 – 0.20	0.07	-2.47 (1.13)	-4.70 – 0.24	0.03
3	13267A, NCT01140906/ 2011	Placebo	-	-	-	-			
		Vortioxetine	15	-5.53 (1.09)	-7.66 – -3.44	<0.001			
			20	-7.09 (1.08)	-9.21 – -4.97	<0.001			
		Duloxetine	60	-9.45 (1.07)	-11.55 – -7.35	<0.001			

4	304, NCT00672620/ 2008	Placebo	-	-	-	-			
		Vortioxetine	5	-0.08 (1.12)	-2.28 – 2.12	0.94	-0.58 (1.04)	-2.61 – 1.46	0.58
		Duloxetine	60	-2.87 (1.13)	-5.10 – -0.65	0.01	-2.96 (1.05)	-5.02 – -0.91	0.005
5	315, NCT01153009/ 2012	Placebo	-	-	-	-			
		Vortioxetine	15	-1.5(1.21)	-3.86 – 0.91	0.22			
			20	-2.8(1.21)	-5.12 – -0.38	0.02			
		Duloxetine	60	-4.1(1.21)	-6.46 – -1.69	<0.001			
6	NCT01571453, KCT0000432, 13926A/2013	Vortioxetine	10	-1.20 (0.93)	-3.03 – 0.63	0.19			
		Venlafaxine	150	-	-	-			
7	12541A, NCT00811252/ 2010	Placebo	-	-	-	-			
		Vortioxetine	5	-4.29 (1.03)	-6.32 – -2.26	<0.001	-3.32 (1.01)	-5.31 – -1.34	<0.001
		Duloxetine	60	-6.83 (1.05)	-8.89 – -4.78	<0.001	-5.48 (1.03)	-7.50 – -3.46	<0.001
8	305, NCT00735709/ 2009	Placebo	-	-	-	-			
		Vortioxetine	5	-4.18 (1.00)	-6.14 – -2.22	<0.001	-4.12 (1.04)	-6.17 – -2.08	-
			10	-4.75 (1.01)	-6.74 – -2.76	<0.001	-4.93 (1.05)	-6.99 – -2.86	<0.001
9	316, NCT01163266 /2012	Placebo	-	-	-	-			
		Vortioxetine	10	-2.19 (1.15)	-4.45 – 0.08	0.058			
			20	-3.64 (1.16)	-5.92 – -1.35	0.002			
10	303, NCT00672958 /2008	Placebo	-	-	-	-			
		Vortioxetine	5	-0.32 (0.95)	-2.19 – 1.55	0.74	-0.74 (0.89)	-2.48 – 1.01	0.41
11	317, NCT01179516/ 2012	Placebo	-	-	-	-			
		Vortioxetine	10	-0.79 (1.49)	-3.71 – 2.14	0.60			
			15	-0.49 (1.50)	-3.44 – 2.46	0.75			

Table 2-5 Safety outcomes (1) incidence of serious adverse events (any serious TEAE: treatment-emergent adverse event) (2) incidence of adverse events leading to discontinuation (any TEAE: treatment-emergent adverse event, leading to discontinuation)

ID	Study name/year	Drug name	Prescribed dose (mg)	Sample size	(1) Incidence of serious adverse events (any serious TEAE: treatment-emergent adverse event) n(%)	(2) Incidence of adverse events leading to discontinuation (any TEAE: treatment-emergent adverse event, leading to discontinuation) n (%)
1	11492A, NCT00839423/2007	Placebo	-	105	0	4(4)
		Vortioxetine	5	108	0	3(3)
			10	100	2(2)	7(7)
		Venlafaxine	225	113	1(1)	16(14)
2	11984A, NCT00635219/2009	Placebo	-	148	3(2)	12(8)
		Vortioxetine	2.5	155	1(0.7)	10(6)
			5	157	3(2)	18(11)
			10	151	2(1)	15(10)
		Duloxetine	60	155	2(1)	19(13)
3	13267A, NCT01140906/2011	Placebo	-	158	0	7(4)
		Vortioxetine	15	151	0	10(7)
			20	151	2(1)	17(11)
		Duloxetine	60	147	3(2)	7(5)
4	304, NCT00672620/2008	Placebo	-	151	2(1)	8(5)
		Vortioxetine	5	153	3(2)	13(9)
		Duloxetine	60	150	2(1)	16(11)
5	315, NCT01153009/2012	Placebo	-	159	0	5(3)
		Vortioxetine	15	147	2(1)	14(10)
			20	154	0	14(9)
		Duloxetine	60	150	0	11(7)
6	NCT01571453, KCT0000432, 13926A/2013	Vortioxetine	10	211	2(1)	14(7)
		Venlafaxine	150	226	8(4)	32(14)

7	12541A, NCT00811252/2010	Placebo	-	145	4(3)	6(4)
		Vortioxetine	5	156	1(1)	10(6)
		Duloxetine	60	151	1(1)	15(10)
8	305, NCT00735709/2009	Placebo	-	140	2(1)	2(1)
		Vortioxetine	5	140	1(1)	1(1)
			10	139	2(1)	5(4)
9	316, NCT01163266 /2012	Placebo	-	157	0	2(1)
		Vortioxetine	10	155	2(1)	9(6)
			20	150	0	7(5)
10	303, NCT00672958 /2008	Placebo	-	298	4(1)	9(3)
		Vortioxetine	5	299	7(2)	9(3)
11	317, NCT01179516/2012	Placebo	-	160	1(1)	6(4)
		Vortioxetine	10	154	1(1)	8(5)
			15	151	0	12(8)

Table 2-6 Summary of the clinical studies published after the latest clinical studies included in the previously reported systematic reviews

Study name, bibliographic information	CCT002 (26) Nishimura et al (2018) ClinicalTrials.gov Identifier: NCT01255787	CCT 003 (27) Inoue et al (2018) ClinicalTrials.gov Identifier: NCT01395147	CCT 004 (28) Inoue et al (2020) ClinicalTrials.gov Identifier: NCT02389816
	Trintellix Tablets 10 mg, Trintellix Tablets 20 mg, Review Report (29) and Interview Form (30)		
Study period	November 2010 to April 2012	May 2011 to December 2012	April 2015 to March 2018
Study design	Randomized controlled study	Randomized controlled study	Randomized controlled study
Sample size	593 subjects (151 subjects in the placebo group, 144 subjects in the vortioxetine 5 mg group, 148 subjects in the vortioxetine 10 mg group, and 150 subjects in the vortioxetine 20 mg group)	366 subjects (124 subjects in the placebo group, 119 subjects in the vortioxetine 5 mg group, and 123 subjects in the vortioxetine 10 mg group)	493 subjects (164 subjects in the placebo group, 165 subjects in the vortioxetine 10 mg group, and 164 subjects in the vortioxetine 20 mg group)
Eligibility criteria	· Patients mainly diagnosed with major depressive disorder according to DSM-IV-TR · Patients aged between 20 and 64 years · Patients with current major depressive episodes ≥3 months at screening · Patients with a MADRS total score ≥26 and a Clinical Global Impressions-Severity (CGI-S) score ≥4	· Patients mainly diagnosed with major depressive disorder according to DSM-IV-TR · Patients aged between 20 and 75 years · Patients with current major depressive episodes ≥3 months at the start of run-in period · Patients with a MADRS total score ≥26 and a Clinical Global Impressions-Severity (CGI-S) score ≥4	· Patients mainly diagnosed with recurrent major depressive disorder according to DSM-IV-TR · Patients aged between 20 and 75 years · Patients with current major depressive episodes ≥3 and ≤12 months · Patients with a MADRS total score ≥26, a HAM-D17 total score ≥18, and a CGI-S score ≥4

Exclusion criteria	· Patients who have concurrent psychiatric disorders other than major depressive disorder (however, those with anxiety symptoms will also be eligible for the study unless they meet the diagnostic criteria for anxiety disorder as defined by DSM-IV-TR) · Patients who have concurrent or a history of manic or hypomanic episodes, schizophrenia, or other psychotic disorders as defined by DSM-IV-TR (including major depressive disorder with psychotic features, mental retardation, an organic mental disorder, or a psychiatric disorder accompanied by general somatic disorders) · Patients with DSM-IV-TR Axis II disorders that could potentially affect evaluation of the study results	· Patients who have concurrent psychiatric disorders other than major depressive disorder as defined by DSM-IV-TR · Patients who have concurrent or a history of manic or hypomanic episodes, schizophrenia, or other psychotic disorders as defined by DSM-IV-TR (including major depressive disorder with psychotic features, mental retardation, an organic mental disorder, or a psychiatric disorder accompanied by general somatic disorders) · Patients with DSM-IV-TR Axis II disorders that could potentially affect evaluation of the study results	· Patients who have concurrent psychiatric disorders other than major depressive disorder as defined by DSM-IV-TR · Patients who have concurrent or a history of manic, mixed, or hypomanic episodes, major depressive disorder with psychotic features, schizophrenia, or other psychotic disorders as defined by DSM-IV-TR (including substance-related mental disorder or a psychiatric disorder accompanied by general somatic disorders) · Patients who have experienced an inadequate response to a sufficient amount of two or more antidepressants for at least 6 weeks for the treatment of current or past major depressive episodes · Patients who have undergone escalated drug therapy (i.e., the addition of lithium, triiodothyronine/thyroxine, lamotrigine, valproic acid, carbamazepine, or atypical antipsychotics, or concomitant use of antidepressants) for the treatment of current major depressive episodes · Patients who have undergone electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial magnetic stimulation within 6 months of the run-in period

			・ Patients who are receiving cognitive behavior therapy or psychotherapy at the time of informed consent, or are scheduled to receive treatment during the study period
Method of administration	Administer one tablet of vortioxetine 5, 10, or 20 mg or a placebo once daily for 8 weeks.	Administer one tablet of vortioxetine 5 or 10 mg or a placebo once daily for 8 weeks. Observation period (1): Administer one tablet of the placebo once daily for 2 weeks. Observation period (2): Follow-up for 2 weeks	Placebo lead-in period: Administer one tablet of a placebo once daily for 1 week. Treatment period: Administer one tablet of vortioxetine 10 or 20 mg or the placebo once daily for 8 weeks. • Patients who experienced an improvement or reduction in their MADRS total score ≥25% during the placebo lead-in period are excluded from randomization during the treatment period.
Efficacy outcomes	Primary endpoint: Change from baseline in MADRS total score at Week 8 Secondary endpoints: MADRS response and remission rates at Week 8	Primary endpoint: Change from baseline in MADRS total score at Week 8 Secondary endpoints: MADRS response and remission rates at Week 8 and change from baseline in Hamilton Depression Rating Scale 17 item (HAM-D17) total score	Primary endpoint: Change from baseline in MADRS total score at Week 8 Secondary endpoints: MADRS response and remission rates at Week 8 and change from baseline in HAM-D17 total score
Safety	・ Adverse events, laboratory tests (hematology, blood biochemistry, and urinalysis), vital signs, 12-lead ECG, body weight, and physical examination ・ Suicidal ideation or suicidal behavior (evaluation using the Columbia-Suicide Severity Rating Scale [C-SSRS])	・ Adverse events, laboratory tests (hematology, blood biochemistry, and urinalysis), vital signs, 12-lead ECG, body weight, and physical examination ・ Suicidal ideation or suicidal behavior (evaluation using the Columbia-Suicide Severity Rating Scale [C-SSRS])	・ Adverse events, laboratory tests (hematology, blood biochemistry, and urinalysis), vital signs, 12-lead ECG, and body weight ・ Suicidal ideation or suicidal behavior (evaluation using the C-SSRS)
Results (efficacy)	・ The changes from baseline in the MADRS total score at Week 8 were −13.99 in the placebo group,	・ When analyzed using ANCOVA, the changes from baseline in the MADRS total score at Week 8 were	・ The changes from baseline in the MADRS total score at Week 8 were −12.37 in the placebo group, −15.03

	−14.61 in the vortioxetine 5 mg group, −15.68 in the vortioxetine 10 mg group, and −15.82 in the vortioxetine 20 mg group. · The point estimates of the differences between the vortioxetine 5, 10, and 20 mg groups and the placebo group (each vortioxetine group – placebo group) were –0.61, –1.69, and –1.82, respectively. · There were no statistically significant differences among the treatment groups.	−13.81 in the placebo group, −15.84 in the vortioxetine 5 mg group, and −14.85 in the vortioxetine 10 mg group. · The point estimates of the differences between the vortioxetine 5 or 10 mg groups and the placebo group were –2.03 and –1.04, respectively. · There were no statistically significant differences between the treatment groups.	(p=0.0080) in the vortioxetine 10 mg group, and −15.45 (p=0.0023) in the vortioxetine 20 mg group. · Analysis was performed using a mixed-effects model for measures over time, with change from baseline in the MADRS total score as a dependent variable and evaluation time point, treatment group, interaction of treatment group with evaluation time point, and interaction of baseline MADRS total score with evaluation time point as fixed effects.
Results (safety)	· The incidence of adverse event was 40.4% (61/151 subjects) in the placebo group, 47.2% (68/144 subjects) in the vortioxetine 5 mg group, 48.6% (72/148 subjects) in the vortioxetine 10 mg group, and 56.7% (85/150 subjects) in the vortioxetine 20 mg group. · Adverse event that occurred in the vortioxetine 5, 10, or 20 mg groups with an incidence of ≥5% were nausea, dry mouth, headache, and dizziness. Serious adverse event occurred in 2 subjects: suicide attempt and suicidal ideation reported in 1 subject in the vortioxetine 20 mg group, and abortion missed in 1 subject in the vortioxetine 20 mg group.	· The incidence of adverse event was 33.1% (41/124 subjects) in the placebo group, 41.2% (49/119 subjects) in the vortioxetine 5 mg group, and 57.4% (70/122 subjects) in the vortioxetine 10 mg group. Adverse event that occurred in the vortioxetine 5 or 10 mg groups with an incidence of ≥5% were nausea, diarrhea, somnolence, and headache. · The incidence of severe adverse event was 0.8% (1/124 subjects) in the placebo group, 0.8% (1/119 subjects) in the vortioxetine 5 mg group, and 0% in the vortioxetine 10 mg group. · A serious adverse event was suicidal behaviour reported in 1	· Major adverse event (those with an incidence of ≥5%) were nausea reported in 1 (0.6%), 20 (12.1%), and 25 (15.3%) subjects, respectively, in the placebo, vortioxetine 10 mg, and vortioxetine 20 mg groups, vomiting in 0 (0%), 9 (5.5%), and 4 (2.5%) subjects, respectively, and somnolence in 6 (3.7%), 7 (4.2%), and 11 (6.7%) subjects, respectively. · Adverse event leading to treatment discontinuation were headache, akathisia, and sleep attacks in 1 subject each in the placebo group, vomiting in 3 subjects, and headache and insomnia in 1 subject each in the vortioxetine 10 mg group, and vomiting in 3 subjects and abdominal discomfort and

	· The incidence of adverse event leading to discontinuation was 2.0% (3/151 subjects) in the placebo group, 1.4% (2/144 subjects) in the vortioxetine 5 mg group, 5.4% (8/148 subjects) in the vortioxetine 10 mg group, and 4.0% (6/150 subjects) in the vortioxetine 20 mg group.	subject in the vortioxetine 10 mg group. · The incidence of adverse event leading to discontinuation was 2.4% (3/124 subjects) in the placebo group, 0.8% (1/119 subjects) in the vortioxetine 5 mg group, and 2.5% (3/122 subjects) in the vortioxetine 10 mg group.	nausea in 1 subject each in the vortioxetine 20 mg group. · A serious adverse event, including death, was cerebral hemorrhage reported in 1 subject (fatal) in the vortioxetine 20 mg group. · The incidence of adverse events was 13.0%, 24.8%, and 26.4%, respectively, in the placebo, vortioxetine 10 mg, and vortioxetine 20 mg groups between Day 1 and Day 7.

2.1.7.1 Summary of clinical trials

As shown in Tables 2-3 to 2-6, the distribution of patient characteristics (such as age, medical history, severity at baseline, and whether recurrent major depressive disorder is studied) in the clinical studies evaluating vortioxetine included in the study by Cipriani et al. (2018) varies across the studies. Of 11 studies, 7 were active-controlled studies and the rest were placebo-controlled. Four of the studies demonstrated a statistically significant difference in the primary outcome, improvement in depressed state. In contrast, no significant differences were found in 5 of the studies, and a significant difference was detected only in the maximum dose group in the remaining two studies.

Phase 3 studies have been conducted three times in Japan so far: CCT002 and CCT003 in patients with MDD demonstrated no statistically significant differences in improvement in depressed state compared to the placebo group. In CCT004, vortioxetine was evaluated in patients with “recurrent major depressive disorder” characterized by the recurrence of depressive episodes, and patients who experienced an improvement or reduction in their MADRS total score ≥25% during the lead-in period were excluded from randomization during the treatment period. The changes from baseline in the MADRS total score for depression assessment were −12.73 in the placebo group, −15.03 in the vortioxetine 10 mg group, and −15.45 in the vortioxetine 20 mg group, indicating a statistically significant difference.

Patients with mild depression, treatment-resistant depression, comorbid psychiatric disorders, drug abuse, or those who are at risk of suicide are excluded from the overseas and Japanese studies. The outcomes are only verified for short-term acute-phase treatment.

2.2. Summary of evaluation of additional benefit by manufacturer and critique by academic group

According to the report by the manufacturer, for population (a): patients with mild depression or in a mild depressed state, no relevant clinical studies were identified. Thus, the manufacturer concluded as “no additional benefit” or “additional benefit cannot be determined”. The academic group reached the same conclusion as the manufacture.

In addition, the manufacturer performed an additional systematic review expanding “intervention” in their search strategy as vortioxetine to new generation antidepressants to assess whether there was other evidence in patients with mild depression or in a mild depressed state as shown in the supplementary material. The manufacturer submitted the results to report that they did not find any clinical studies relevant to this context (dated November 10, 2020).

As for the additional benefit of vortioxetine for population (b): patients with moderate or severe depression or in a moderate or severe depressed state, the manufacturer limited the results of the study by Cipriani et al. (2018) to 8 new generation antidepressants (SSRI, SNRI, and NaSSA) approved in Japan, and performed an additional systematic review of the literature published after the search period for Cipriani et al. by reintegrating the relevant study data for NMA. The results of NMA did not find any clear differences in effect between vortioxetine and other new generation antidepressants. The systematic review performed for the evaluation of additional benefit showed that the results of the manufacturer were consistent with those of the academic group in that the study by Cipriani et al. (2018) was identified as the relevant publication. However, there were discrepancies in the following two aspects of the systematic review between the manufacturer and the academic group:

<Outcome>

The manufacturer included studies that had their primary endpoint as improvement in cognitive function or sexual function, while having improvement in depression state as secondary endpoint. Since the drug was indicated for the treatment of patients with depression or in a depressed state, the academic group included studies focusing on improvement in depressed state as a primary outcome.

<Using indirect comparison based on NMA by Cipriani et al. (2018) >

The evaluation of additional benefit conducted by the manufacturer via NMA updates by Cipriani et al. (2018) has validity for the following reasons:

- The study by Cipriani et al. (2018) does not limit the research questions set by the academic group in that it is conducted to compare the efficacy and safety of 21 different antidepressants prescribed to adult patients with acute-phase major depressive disorder.

- A total of 522 studies were included in the final NMA, and it is the most comprehensive study with new generation antidepressants as comparators, providing a certain level of evidence for the research questions by the academic group.
- The systematic review includes a wider range of databases, such as Cochrane Central, CINAHL, Embase, LILACS, MEDLINE, MEDLINE In-Process, PsycINFO, websites of regulatory authorities, and international clinical study registries, to enroll studies registered by January 8, 2016. Because pair-wise comparison and network meta-analysis are performed using the random effect model for the primary efficacy and safety endpoints, and integrated data are also published, data on the drugs can also be extracted for re-analysis, and the transparency of the data used for the studies is ensured to some extent.

On the other hand, there are some concerns about the use of indirect comparison data from NMA in the evaluation of the additional benefit of vortioxetine for the following reasons:

- Inclusion and exclusion criteria for patients differ among the clinical studies, and there may be a bias in the results of integrated heterogeneity of the studies.
- Of the 522 studies, 46 (9%), 380 (73%), and 96 (18%) were considered high, moderate, and low risk for bias, respectively, and it has been concluded that the certainty of the overall evidence is moderate to very low.
- Only short-term efficacy and safety data collected during the clinical study period are evaluated, lacking evidence of the long-term efficacy and safety.
- With respect to the evaluation period for the outcomes, vortioxetine is evaluated for 6 to 8 weeks in the clinical studies, and results collected at the time point closest to Week 8 are used if data are reported at more than one evaluation time point. However, results may be affected by variation in the data evaluation time between studies because remission and withdrawal rates are more likely to be dependent on time.

2.3 Summary of evaluation of additional benefit by academic group

The results of the evaluation are summarized in Tables 2-7 and 2-8.

Table 2-7 Evaluation of additional benefit for population (a)

Population	Patients with mild depression or in a mild depressed state
Intervention	Vortioxetine
Comparator	No drug treatment
Outcome	Improvement in depressed state
Whether or not additional benefit is shown	☐ Additional benefit is shown ☐ "No additional benefit" or "additional benefit cannot be determined" ■ Impossible to analyze because of the lack of clinical study data used for evaluation
Data used as the basis for the decision	☐ Meta-analysis of RCTs ☐ Single RCT ☐ Prospective, controlled, observational study ☐ Indirect comparison of RCTs ☐ Comparison of single-arm studies ■ No relevant clinical data
Reason for the decision on whether additional benefit is shown	As a result of the systematic review, no clinical studies of vortioxetine were identified, and similar results were also obtained for other new generation antidepressants.

Table 2-8 Evaluation of additional benefit for population (b)

Population	Patients with moderate or severe depression or in a moderate or severe depressed state
Intervention	Vortioxetine
Comparator	SSRI: fluvoxamine, paroxetine, sertraline, and escitalopram SNRI: milnacipran, duloxetine, and venlafaxine NaSSA: mirtazapine
Outcome	Improvement in depressed state
Whether or not additional benefit is shown	☐ Additional benefit is shown ■ "No additional benefit" or "additional benefit cannot be determined" ☐ Impossible to analyze because of the lack of clinical study data used for evaluation
Data used as the basis for the decision	■ Meta-analysis of RCTs (pooled analysis of several RCTs) ☐ Single RCT ☐ Prospective, controlled, observational study ☐ Indirect comparison of RCTs ☐ Comparison of single-arm studies ☐ No relevant clinical data
Reason for the decision on whether additional benefit is shown	Considering the results of direct and indirect comparison studies, there is no significant difference in treatment effect between vortioxetine and other new generation antidepressants.

3. Evaluation of cost-effectiveness

3.1. Summary of analysis by manufacture

The manufacturer performed a cost-minimization analysis on the assumption that vortioxetine had no additional benefit compared to other new generation antidepressants. In the cost-minimization analysis, a decision tree model showing the pathology of depression or depressed state (acute phase, maintenance phase, and recovery phase) and a Markov model-based model were used (Figures 3-1 and 3-2). The population of the analysis was patients with moderate or severe depression or in a moderate or severe depressed state. The population was classified into two groups: those receiving first-line treatment ([redacted]%) and those receiving second-line treatment ([redacted]%). The duration of the analysis was 1 year. The drug costs and the consultation fees were estimated in the first-line and second-line treatment populations, and then weighted averages were calculated from individual analysis results.

The main assumptions in the model used for analysis were as follows:

- The daily drug price of milnacipran is used as the drug cost of the comparator in the base case analysis.
- The daily drug prices of new generation antidepressants other than milnacipran (venlafaxine, escitalopram, and duloxetine) are used in the sensitivity analysis.
- Dose titration is not considered.
- The mean prescribed dose is considered in selecting the drug costs.
- The duration of remission is 8 weeks for antidepressant treatment.
- Patients recover from depression or depressed state when they have achieved remission for 6 months and their symptoms do not recur after attainment of remission (for a maximum of 4 months during the analysis period).
- Only remission rates after treatment switch and recurrence rates after remission in the Markov model differ between the first-line and second-line treatment populations. Other settings are identical between these populations.
- Only the drug costs differ between vortioxetine and the comparator. Other settings between them are identical.

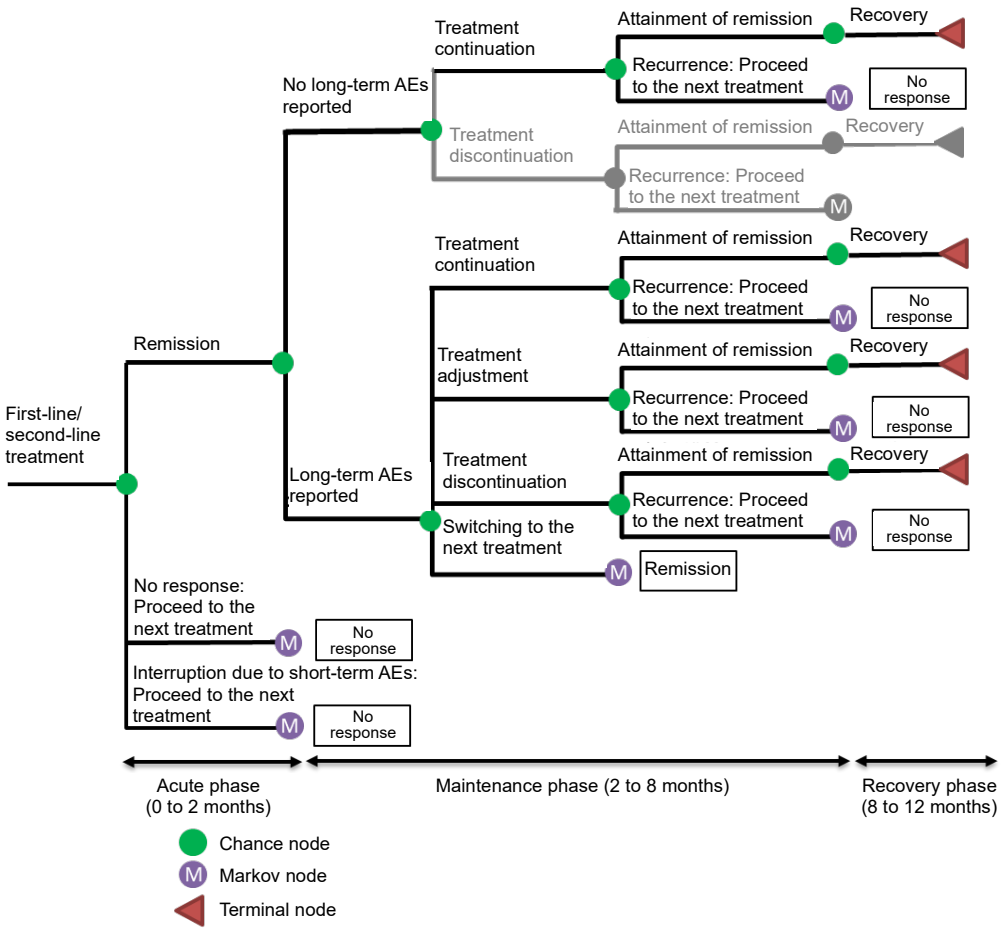

Figure 3-1 Model for the transition until switching to the next treatment (decision tree model) [(31)]

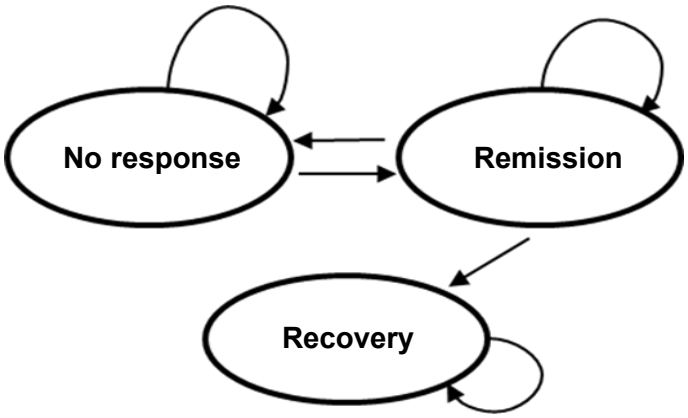

Figure 3-2 Model for the transition after switching to the next treatment (Markov model, 2-month cycle) [(31)]

The results of the base case analysis by the manufacturer were summarized as shown in Tables 3-1 and 3-2, and there was a cost increase of 16,053 yen for vortioxetine.

Table 3-1 Results of the base case analysis (comparison with milnacipran)

	Total cost (yen)	Incremental cost (yen)
Vortioxetine	274,454	16,053
Comparator	258,401	-

Table 3-2 Detailed breakdown of costs

	Vortioxetine	Comparator
Drug cost of vortioxetine (yen)	[redacted]	[redacted]
Drug cost of milnacipran (yen)	[redacted]	[redacted]
Drug cost after treatment switch (yen)	[redacted]	[redacted]
Consultation (status) fees (yen)	[redacted]	[redacted]

Sensitivity analyses are shown in Tables 3-3 to 3-8.

Table 3-3 Results of the sensitivity analysis (comparison with venlafaxine)

	Total cost (yen)	Incremental cost (yen)
Vortioxetine	267,128	-14,521
Comparator	281,648	-

Table 3-4 Detailed costs

	Vortioxetine	Comparator
Drug cost of vortioxetine (yen)	[redacted]	[redacted]
Drug cost of venlafaxine (yen)	[redacted]	[redacted]
Drug cost after treatment switch (yen)	[redacted]	[redacted]
Consultation (status) fees (yen)	[redacted]	[redacted]

Table 3-5 Results of the sensitivity analysis (comparison with escitalopram)

	Total cost (yen)	Incremental cost (yen)
Vortioxetine	261,177	-1,030
Comparator	262,207	-

Table 3-6 Detailed costs

	Vortioxetine	Comparator
Drug cost of vortioxetine (yen)	[redacted]	[redacted]
Drug cost of escitalopram (yen)	[redacted]	[redacted]
Drug cost after treatment switch (yen)	[redacted]	[redacted]
Consultation (status) fees (yen)	[redacted]	[redacted]

Table 3-7 Results of the sensitivity analysis (comparison with duloxetine)

	Total cost (yen)	Incremental cost (yen)
Vortioxetine	271,391	-2,771
Comparator	274,162	-

Table 3-8 Detailed costs

	Vortioxetine	Comparator
Drug cost of vortioxetine (yen)	[redacted]	[redacted]
Drug cost of duloxetine (yen)	[redacted]	[redacted]
Drug cost after treatment switch (yen)	[redacted]	[redacted]
Consultation (status) fees (yen)	[redacted]	[redacted]

3.1.1 Critique on manufacture's analysis

Since no additional benefit was suggested in the earlier section (2-3), it is appropriate to perform a cost-minimization analysis, assuming that there is no difference in treatment effect between vortioxetine and other new generation antidepressants.

In the cost-minimization analysis done by the manufacture, healthcare costs was estimated by using a decision tree model and a Markov model to show the pathology of depression or depressed state. Although health technology assessment agencies in foreign countries have used similar model structures for cost-effectiveness analyses to evaluate vortioxetine, these models have not been utilized for cost-minimization analyses (1)(2)(5).

As for the method of the cost-minimization analysis submitted by the manufacturer, the following points need to be addressed:

- The major issue is the estimation of the drug cost in this analysis because health resource consumption is the same for vortioxetine and comparator other than the price of drug itself.

- The drug costs in the model is estimated by multiplying the daily drug costs by the duration of treatment, and the duration of treatment (resulting differences in drug costs) depends on the structure of the decision tree model, probability parameters, and settings for the duration of treatment in each scenario (Figure 3-3).
- Comparison of the daily drug costs suffices for the cost-minimization analysis, because the duration of treatment does not differ between vortioxetine and other new generation antidepressants.

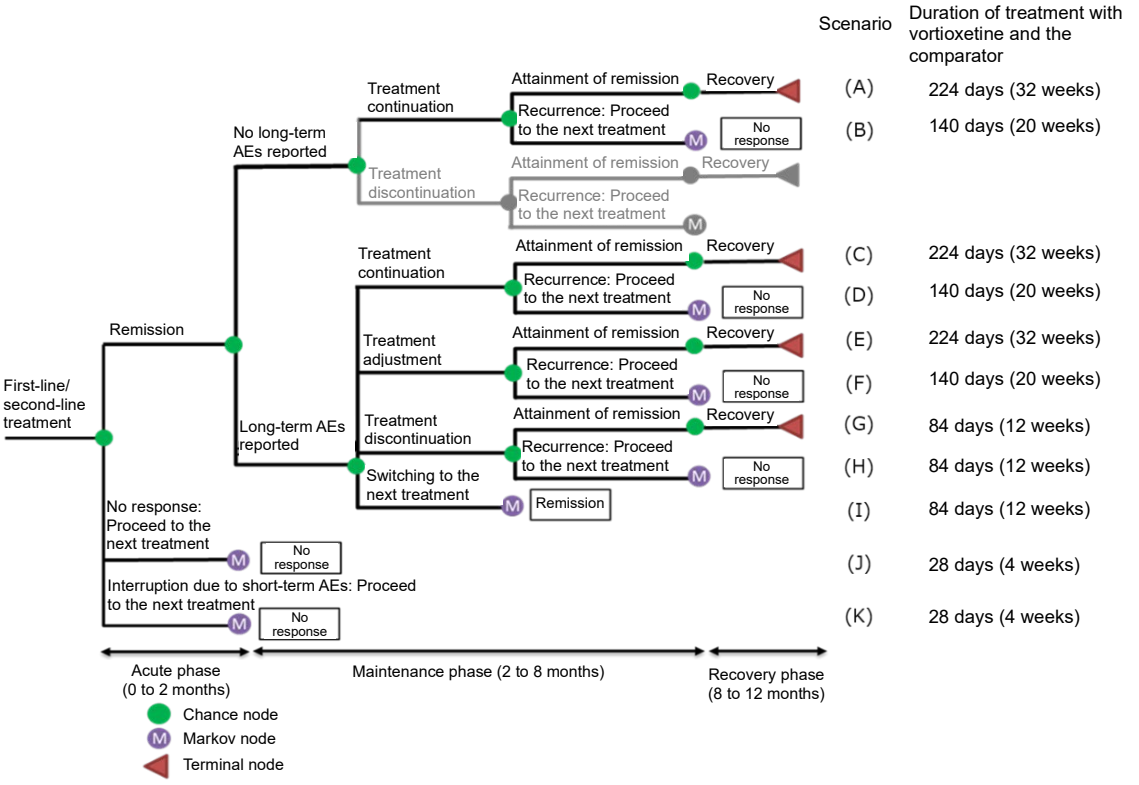

Figure 3-3 Structure of the decision tree model and duration of treatment in each scenario

*The names of the scenarios and duration of treatment were added by the academic group.

<Settings for probability parameters>

For the estimation, the manufacturer integrated the values reported in the study of vortioxetine and milnacipran, in which milnacipran was selected as the comparator in the base case analysis, and probability parameters (remission rates and rates of treatment discontinuation due to AEs) for the decision tree model were included in NMA. The following points need to be noted for the above study:

- Using different comparators is associated with varying remission rates and treatment discontinuation rates due to AEs for vortioxetine, making it difficult to interpret the results from the base case analysis and sensitivity analysis.
- The evaluation of vortioxetine has indicated no additional benefit of vortioxetine compared to other new generation antidepressants; therefore, it is appropriate to estimate remission rates and rates of treatment discontinuation due to AEs by integrating the values reported in all clinical studies included in NMA.
- There is uncertainty about estimating the duration of treatment using models because the evaluation time points for remission rates and rates of treatment discontinuation due to AEs are in the range of 6 to 8 weeks in each clinical study.

<Settings for the duration of treatment>

The manufacturer assumed that patients who had achieved remission in the acute phase (2 months) would have recovered from depression or depressed state when they had achieved remission for 6 months, and their symptoms would not recur after attainment of remission (for a maximum of 4 months during the analysis period) (Figure 3-3). In other scenarios, analysis was also performed according to some hypotheses about the duration of treatment with vortioxetine and the comparator (Figure 3-3). The following points need to be addressed:

- The manufacturer reports that, “the duration of treatment should be at least 4 to 9 months after remission for an initial manifestation, and at least 2 years for a recurrence, and the dose should be the same as that used for acute treatment (p.16)” (31), and therefore, the duration of treatment may be underestimated.
- The mean duration of treatment based on the model submitted by the manufacturer is 89.2 days; however, to date, no data are available on the duration of treatment with vortioxetine in clinical practice, and there is uncertainty about the settings for the duration of treatment (Figure 3-4).

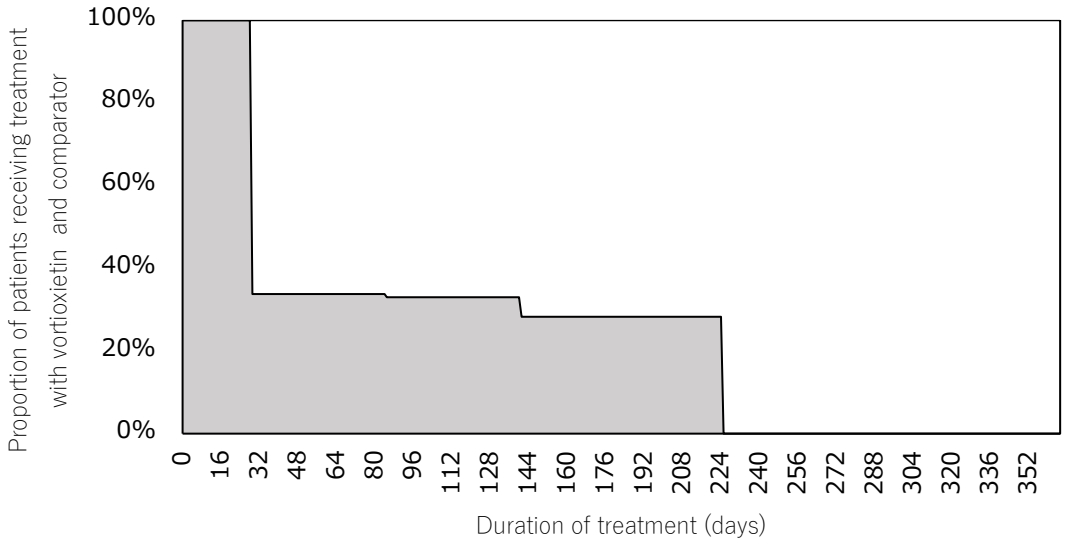

Figure 3-4 Distribution of the duration of treatment in the model submitted by the manufacturer

(Mean duration of treatment = 89.2 days)

3.2 Summary of revision by academic group

<Base case analysis>

- Perform a cost-minimization analysis, assuming that the effects are similar among vortioxetine and other new generation antidepressants.
- Estimate costs using the drug price of milnacipran, which is the cheapest drug of all the other new generation antidepressants selected as comparator because the superiority or inferiority of these drugs has not been indicated.
- Compare the daily drug price, because no studies have shown that the duration of treatment and health resource consumption, other than the relevant drug price itself, differ among vortioxetine and the comparators.

<Sensitivity analysis>

- Perform sensitivity analyses considering the drug prices of new generation antidepressants other than milnacipran.

Methods for revied analysis

- Estimate the daily drug price from the drug price per mg and the mean prescribed dose (mg) of commonly used specifications for vortioxetine and other new generation antidepressants.
- For the mean prescribed dose (mg) of vortioxetine and other new generation antidepressants, we use the claim data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan.
    - Patients to whom the ICD-10 code (F32, depressive episode; F33, recurrent depressive disorder) corresponding to depression or depressed state was assigned in medical claims and DPC admission claims during the analysis period (medical treatment given between April 1, 2019 and March 31, 2020) were extracted. The exclusion criteria were claims with flags for suspicious illness and those involving patients aged <20 years on the day of the first medical treatment recorded during the analysis period. Prescriptions found in the medical (not hospitalized) and pharmacist's fee claims recorded for the above patients were counted when they included the anti-depressants shown in Attached Table S-3. The prescription was excluded when it included two or more generic names of different categories for antidepressants.

For the calculation of the daily mean prescribed dose, the number of drugs included in a prescription was counted by generic name during the analysis period. The prescription was issued for the same patient in the same claim on the same date. For the calculation of the daily mean prescribed dose, the sum of the drug usage multiplied by the amount of ingredient per tablet for the same genetic name in the same prescription was used to determine the mean dose.

4. Revised analysis by academic group

4.1 Base case analysis

By using the National Database of Health Insurance Claims and Specific Health Checkups of Japan, the data on 2,432,892 patients, and 38.8% of them were male with a mean age of 55.8 years were obtained. The results of the mean daily prescribed dose are shown in Table 4-1.

Table 4-1 Daily mean prescribed dose of the new generation antidepressants

Medicine category	Generic name	Starting dose indicated on the package insert (mg)	Maximum dose indicated on the package insert (mg)	No. of prescriptions	%	Daily prescribed dose Mean (mg)	Daily prescribed dose Standard deviation (mg)
				18,873,484	-		
SSRI	Fluvoxamine	50	150	1,514,316	8.0%	75.2	59.8
	Paroxetine	10-20 (tablets) 12.5 (CR tablets)	40 (tablets) 50 (CR tablets)	3,268,647	17.3%	19.1	14.8
	Sertraline	25	100	3,076,447	16.3%	49.8	32.8
	Escitalopram	10	20	3,158,921	16.7%	11.9	6.6
SNRI	Milnacipran	25	100	447,274	2.4%	50.1	38.0
	Duloxetine	20	60	3,752,168	19.9%	35.1	18.7
	Venlafaxine	37.5	225	862,909	4.6%	115.3	67.9
NaSSA	Mirtazapine	15	45	2,738,212	14.5%	20.3	22.0
Others	Vortioxetine	10	20	54,590	0.3%	13.5	7.3

The results of the re-analysis of the base case analysis are presented in Table 4-2. The comparison of the daily drug price revealed that the drug price of vortioxetine was 186.23 yen higher than milnacipran.

Table 4-2 Cost-minimization analysis of vortioxetine versus milnacipran

	Unit Drug price (yen)*	Mean prescribed dose (mg)	Daily drug price (yen)	Incremental cost (yen)
Vortioxetine	10 mg 168.90 20 mg 253.40	13.5	228.02	-
Milnacipran	12.5 mg 14.30 15 mg 17.30 25 mg 24.70 50 mg 41.70	50.1	41.78	186.23

*The commonly used specifications are underlined.

*If there was more than one originator drug, the drug with the cheapest unit price was adopted.

4.2 Scenario analysis

The results of the scenario analyses considering the drug prices of new generation antidepressants other than milnacipran are presented in Table 4-3.

Table 4-3 Results of the scenario analysis

	Unit Drug price (yen)*	Mean prescribed dose (mg)	Daily drug price (yen)	Incremental cost (yen)
Vortioxetine	10 mg 168.90 20 mg 253.40	13.5	228.02	-
SSRI				
Fluvoxamine	25 mg 28.70 50 mg 48.50 75 mg 65.40	75.2	72.94	155.07
Paroxetine	5 mg (tablets) 42.60 10 mg (tablets) 75.80 20 mg (tablets) 131.70 6.25 mg (CR tablets) 43.70 12.5 mg (CR tablets) 75.40	19.1	115.21	112.80

	25 mg (CR tablets) 130.60			
Sertraline	25 mg (tablets/OD tablets) 79.00 50 mg (tablets/OD tablets) 135.70 100 mg (tablets/OD tablets) 233.80	49.8	157.37	70.65
Escitalopram	10 mg 193.50 20 mg 293.90	11.9	230.27	-2.25
SNRI				
Duloxetine	20 mg 145.20 30 mg 196.60	35.1	254.83	-26.81
Venlafaxine	37.5 mg 141.40 75 mg 237.10	115.3	364.50	-136.49
NaSSA				
Mirtazapine	15 mg 118.30 30 mg 196.20	20.3	160.10	67.92

*The commonly used specifications are underlined.

*If there was more than one originator drug, the drug with the cheapest unit price was adopted.

4.3 Summary results

The summary result of revised analysis of vortioxetine is shown in Tables 4-3 and 4-4.

Table 4-3 Summary of revised analysis result of population (a)

Population	Patients with mild depression or in a mild depressed state
Comparator	No drug treatment
Reference value for ICER	■ Regular product ☐ Product requiring special consideration
Interval to which the ICER is most likely to belong	☐ Cost reduction or dominant ☐ <5 million yen (<7.5 million yen) ☐ ≥5 million yen (≥7.5 million yen) and <7.5 million yen (<11.25 million yen) ☐ ≥7.5 million yen (≥11.25 million yen) and <10 million yen (<15 million yen) ☐ ≥10 million yen (≥15 million yen) ☐ Comparable (or inferior in) effect and higher cost ■ Impossible to analyze because of the lack of clinical study data used for evaluation
Reason for the decision	No clinical data available

Table 4-4 Summary of revised analysis result of population (b)

Population	Patients with moderate or severe depression or in a moderate or severe depressed state
Comparator	The cheapest drug (milnacipran) of the new generation antidepressants (SSRI, SNRI, and NaSSA)
Reference value for ICER	■ Regular product ☐ Product requiring special consideration
Interval to which the ICER is most likely to belong	☐ Cost reduction or dominant ☐ <5 million yen (<7.5 million yen) ☐ ≥5 million yen (≥7.5 million yen) and <7.5 million yen (<11.25 million yen) ☐ ≥7.5 million yen (≥11.25 million yen) and <10 million yen (<15 million yen)

	□ ≥10 million yen (≥15 million yen) ■ Comparable (or inferior in) effect and higher cost □ Impossible to analyze because of the lack of clinical study data used for evaluation
Reason for the decision	The cost of vortioxetine increases by 186.23 yen per day compared to milnacipran.

4.4 Weight of price adjustment rate

The manufacturer reported the proportion of each population for analysis based on a prospective observational study on functional outcomes for MDD (PERFORM-J). In the PERFORM-J, the severity of MDD in 518 patients was evaluated according to MADRS and 109, 312, 95, and 2 patients were rated as mild, moderate, severe, and not applicable, respectively. Based on this result, the manufacturer excluded the 2 patients rated as not applicable from the population for analysis, and calculated the proportion of 516 patients by severity: 21.1% (109/516) of patients were rated mild and 78.9% ([312+95]/516) were rated moderate or severe. The academic group accepted the validity of the manufacturer's view, and considered it appropriate to use 21.1% for mild and 78.9% for moderate or severe cases as the proportion of patients in each population for analysis.

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6. Supplementary material

<Additional systematic review by the manufacturer>

To examine the additional benefit of vortioxetine and other new generation antidepressants for no drug treatment in patients with mild depression or in a mild depressed state, the manufacturer selected I from the PICO framework for the systematic review, and focused on all new generation antidepressants.

- Research questions

Research questions about this examination are as shown in Table S-1.

Table S-1 Research questions for the additional systematic review of the mild population by the manufacturer

Item	Description
Population	Patients with mild depression or in a mild depressed state[1]
Intervention	Vortioxetine SSRI: fluvoxamine, paroxetine, sertraline, and escitalopram SNRI: milnacipran, duloxetine, and venlafaxine NaSSA: mirtazapine
Comparator	No drug treatment[2]
Outcomes	- Improvement in depressed state (remission and response rates) - Tolerability (rate of treatment discontinuation)
Study design	Double-blind RCTs
Period of literature search	From the start of collection of the relevant database to [redacted]

[1] In principle, patients “with depression or in a depressed state” refers to those with MDD as defined by DSM.

[2] “No drug treatment” is defined as continuing consultation with a healthcare professional without any pharmacological interventions.

- Examination method

The examination was performed according to the following steps:

(1) Of the clinical studies adopted according to the inclusion and exclusion criteria shown in Table S-2, those including a placebo are extracted. As with the systematic review of patients with moderate or severe depression or in a moderate or severe depressed state, the results from the systematic reviews performed on the literature published before January 8, 2016 (systematic review using the report by Cipriani et al. [2018]) and those published after [redacted] (additional systematic review) are utilized.

Table S-2 Inclusion and exclusion criteria for the additional systematic review of the mild population by the manufacturer

Item	Inclusion criteria	Exclusion criteria
Language	English and Japanese	
Population	Adult (≥18 years) patients with MDD	
Study design and type of publication	Double-blind RCTs	- Unpublished literature - Abstracts - Studies that include 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression
Treatment	- Vortioxetine - Fluvoxamine - Paroxetine - Sertraline - Escitalopram - Milnacipran - Duloxetine - Venlafaxine - Mirtazapine - Placebo	
Outcomes	- Improvement in depressed state (remission and response rates) - Tolerability (rate of treatment discontinuation)	

(2) As for the inclusion criteria and baseline values in each relevant study in (1), severity is evaluated by reference to the severity scale, MADRS, HAMD17, CGI-S, and QIDS-SR.
(3) Based on the severity in (2), eligible clinical studies falling under the category of “clinical studies only involving mild cases” are extracted.

- Examination results

Of the 179 clinical studies (167 publications) adopted in the systematic review, those including a placebo were evaluated for severity based on the severity scales, MADRS, HAMD17, CGI-S, and QIDS-SR, revealing that there were no “clinical studies only involving mild cases.”

Table S-3 List of antidepressants to be tabulated

Medicine category	System code for computerized processing of health insurance claims	Medicine name	Generic name
SSRI	610432006	DEPROMEL TABLETS 25 25 mg	Fluvoxamine
SSRI	610432007	DEPROMEL TABLETS 50 50 mg	Fluvoxamine
SSRI	620006991	DEPROMEL TABLETS 75 75 mg	Fluvoxamine
SSRI	610432019	Luvox Tablets 25 25 mg	Fluvoxamine
SSRI	610432020	Luvox Tablets 50 50 mg	Fluvoxamine
SSRI	620007147	Luvox Tablets 75 75 mg	Fluvoxamine
SSRI	621998401	Fluvoxamine Maleate Tablets 25 mg “EMEC”	Fluvoxamine
SSRI	621998501	Fluvoxamine Maleate Tablets 50 mg “EMEC”	Fluvoxamine
SSRI	621998601	Fluvoxamine Maleate Tablets 75 mg “EMEC”	Fluvoxamine
SSRI	622000101	Fluvoxamine Maleate Tablets 25 mg “YD”	Fluvoxamine
SSRI	622000201	Fluvoxamine Maleate Tablets 50 mg “YD”	Fluvoxamine
SSRI	622000301	Fluvoxamine Maleate Tablets 75 mg “YD”	Fluvoxamine
SSRI	622000901	Fluvoxamine Maleate Tablets 25 mg “AMEL”	Fluvoxamine
SSRI	622001001	Fluvoxamine Maleate Tablets 50 mg “AMEL”	Fluvoxamine
SSRI	622001101	Fluvoxamine Maleate Tablets 75 mg “AMEL”	Fluvoxamine
SSRI	622001901	Fluvoxamine Maleate Tablets 25 mg “TCK”	Fluvoxamine
SSRI	622002001	Fluvoxamine Maleate Tablets 50 mg “TCK”	Fluvoxamine
SSRI	622002101	Fluvoxamine Maleate Tablets 75 mg “TCK”	Fluvoxamine
SSRI	622004401	Fluvoxamine Maleate Tablets 25 mg “TAKATA”	Fluvoxamine
SSRI	622004501	Fluvoxamine Maleate Tablets 50 mg “TAKATA”	Fluvoxamine
SSRI	622004601	Fluvoxamine Maleate Tablets 75 mg “TAKATA”	Fluvoxamine
SSRI	622007702	Fluvoxamine Maleate Tablets 25 mg “Pfizer”	Fluvoxamine
SSRI	622007802	Fluvoxamine Maleate Tablets 50 mg “Pfizer”	Fluvoxamine
SSRI	622007902	Fluvoxamine Maleate Tablets 75 mg “Pfizer”	Fluvoxamine
SSRI	622010601	Fluvoxamine Maleate Tablets 25 mg “SAWAI”	Fluvoxamine
SSRI	622010701	Fluvoxamine Maleate Tablets 50 mg “SAWAI”	Fluvoxamine
SSRI	622010801	Fluvoxamine Maleate Tablets 75 mg “SAWAI”	Fluvoxamine
SSRI	622018101	Fluvoxamine Maleate Tablets 25 mg “CH”	Fluvoxamine
SSRI	622018201	Fluvoxamine Maleate Tablets 50 mg “CH”	Fluvoxamine
SSRI	622018301	Fluvoxamine Maleate Tablets 75 mg “CH”	Fluvoxamine
SSRI	622020302	Fluvoxamine Maleate Tablets 25 mg “TYK”	Fluvoxamine
SSRI	622020402	Fluvoxamine Maleate Tablets 50 mg “TYK”	Fluvoxamine

SSRI	622020502	Fluvoxamine Maleate Tablets 75 mg “TYK”	Fluvoxamine
SSRI	622021101	Fluvoxamine Maleate Tablets 25 mg “FFP”	Fluvoxamine
SSRI	622021201	Fluvoxamine Maleate Tablets 50 mg “FFP”	Fluvoxamine
SSRI	622021301	Fluvoxamine Maleate Tablets 75 mg “FFP”	Fluvoxamine
SSRI	622022701	Fluvoxamine Maleate Tablets 25 mg “JG”	Fluvoxamine
SSRI	622022801	Fluvoxamine Maleate Tablets 50 mg “JG”	Fluvoxamine
SSRI	622022902	Fluvoxamine Maleate Tablets 75 mg “JG”	Fluvoxamine
SSRI	622031101	Fluvoxamine Maleate Tablets 25 mg “KYORIN”	Fluvoxamine
SSRI	622031201	Fluvoxamine Maleate Tablets 50 mg “KYORIN”	Fluvoxamine
SSRI	622031301	Fluvoxamine Maleate Tablets 75 mg “KYORIN”	Fluvoxamine
SSRI	622032501	Fluvoxamine Maleate Tablets 25 mg “NP”	Fluvoxamine
SSRI	622032601	Fluvoxamine Maleate Tablets 50 mg “NP”	Fluvoxamine
SSRI	622032701	Fluvoxamine Maleate Tablets 75 mg “NP”	Fluvoxamine
SSRI	622035001	Fluvoxamine Maleate Tablets 25 mg “Nichi-Iko”	Fluvoxamine
SSRI	622035101	Fluvoxamine Maleate Tablets 50 mg “Nichi-Iko”	Fluvoxamine
SSRI	622035201	Fluvoxamine Maleate Tablets 75 mg “Nichi-Iko”	Fluvoxamine
SSRI	622055001	Fluvoxamine Maleate Tablets 25 mg “TOWA”	Fluvoxamine
SSRI	622055101	Fluvoxamine Maleate Tablets 50 mg “TOWA”	Fluvoxamine
SSRI	622055201	Fluvoxamine Maleate Tablets 75 mg “TOWA”	Fluvoxamine
SSRI	610443045	Paxil Tablets 10 mg	Paroxetine
SSRI	610443046	Paxil Tablets 20 mg	Paroxetine
SSRI	622003001	Paxil Tablets 5 mg	Paroxetine
SSRI	622135901	Paxil CR Tablets 12.5 mg	Paroxetine
SSRI	622136001	Paxil CR Tablets 25 mg	Paroxetine
SSRI	622659901	Paxil CR Tablets 6.25 mg	Paroxetine
SSRI	622133801	Paroxetine Tablets 5 mg “MEIJI”	Paroxetine
SSRI	622133901	Paroxetine Tablets 10 mg “MEIJI”	Paroxetine
SSRI	622134001	Paroxetine Tablets 20 mg “MEIJI”	Paroxetine
SSRI	622137401	Paroxetine Tablets 10 mg “EE”	Paroxetine
SSRI	622137501	Paroxetine Tablets 20 mg “EE”	Paroxetine
SSRI	622138501	Paroxetine Tablets 10 mg “OHARA”	Paroxetine
SSRI	622138601	Paroxetine Tablets 20 mg “OHARA”	Paroxetine
SSRI	622140801	Paroxetine Tablets 10 mg “KN”	Paroxetine
SSRI	622140901	Paroxetine Tablets 20 mg “KN”	Paroxetine
SSRI	622141401	Paroxetine Tablets 5 mg “TOWA”	Paroxetine

SSRI	622141501	Paroxetine Tablets 10 mg “TOWA”	Paroxetine
SSRI	622141601	Paroxetine Tablets 20 mg “TOWA”	Paroxetine
SSRI	622141701	Paroxetine OD Tablets 10 mg “TOWA”	Paroxetine
SSRI	622141801	Paroxetine OD Tablets 20 mg “TOWA”	Paroxetine
SSRI	622144301	Paroxetine Tablets 5 mg “AMEL”	Paroxetine
SSRI	622144401	Paroxetine Tablets 10 mg “AMEL”	Paroxetine
SSRI	622144501	Paroxetine Tablets 20 mg “AMEL”	Paroxetine
SSRI	622145601	Paroxetine Tablets 5 mg “TAKATA”	Paroxetine
SSRI	622145701	Paroxetine Tablets 10 mg “TAKATA”	Paroxetine
SSRI	622145801	Paroxetine Tablets 20 mg “TAKATA”	Paroxetine
SSRI	622147801	Paroxetine Tablets 5 mg “Pfizer”	Paroxetine
SSRI	622147901	Paroxetine Tablets 10 mg “Pfizer”	Paroxetine
SSRI	622148001	Paroxetine Tablets 20 mg “Pfizer”	Paroxetine
SSRI	622150601	Paroxetine Tablets 5 mg “YD”	Paroxetine
SSRI	622150701	Paroxetine Tablets 10 mg “YD”	Paroxetine
SSRI	622150801	Paroxetine Tablets 20 mg “YD”	Paroxetine
SSRI	622152701	Paroxetine Tablets 5 mg “NISSIN”	Paroxetine
SSRI	622152801	Paroxetine Tablets 10 mg “NISSIN”	Paroxetine
SSRI	622152901	Paroxetine Tablets 20 mg “NISSIN”	Paroxetine
SSRI	622154001	Paroxetine Tablets 5 mg “FFP”	Paroxetine
SSRI	622154101	Paroxetine Tablets 10 mg “FFP”	Paroxetine
SSRI	622154201	Paroxetine Tablets 20 mg “FFP”	Paroxetine
SSRI	622154701	Paroxetine Tablets 5 mg “KOG”	Paroxetine
SSRI	622154702	Paroxetine Tablets 5 mg “NPI”	Paroxetine
SSRI	622154801	Paroxetine Tablets 10 mg “KOG”	Paroxetine
SSRI	622154802	Paroxetine Tablets 10 mg “NPI”	Paroxetine
SSRI	622154901	Paroxetine Tablets 20 mg “KOG”	Paroxetine
SSRI	622154902	Paroxetine Tablets 20 mg “NPI”	Paroxetine
SSRI	622156301	Paroxetine Tablets 5 mg “TCK”	Paroxetine
SSRI	622156401	Paroxetine Tablets 10 mg “TCK”	Paroxetine
SSRI	622156501	Paroxetine Tablets 20 mg “TCK”	Paroxetine
SSRI	622160001	Paroxetine Tablets 5 mg “AA”	Paroxetine
SSRI	622160101	Paroxetine Tablets 10 mg “AA”	Paroxetine
SSRI	622160201	Paroxetine Tablets 20 mg “AA”	Paroxetine
SSRI	622160801	Paroxetine Tablets 5 mg “TANABE”	Paroxetine

SSRI	622160901	Paroxetine Tablets 10 mg “TANABE”	Paroxetine
SSRI	622161001	Paroxetine Tablets 20 mg “TANABE”	Paroxetine
SSRI	622162701	Paroxetine Tablets 5 mg “Chemiphar”	Paroxetine
SSRI	622162801	Paroxetine Tablets 10 mg “Chemiphar”	Paroxetine
SSRI	622162901	Paroxetine Tablets 20 mg “Chemiphar”	Paroxetine
SSRI	622164001	Paroxetine Tablets 5 mg “TSU”	Paroxetine
SSRI	622164101	Paroxetine Tablets 10 mg “TSU”	Paroxetine
SSRI	622164201	Paroxetine Tablets 20 mg “TSU”	Paroxetine
SSRI	622164801	Paroxetine Tablets 5 mg “NP”	Paroxetine
SSRI	622164901	Paroxetine Tablets 10 mg “NP”	Paroxetine
SSRI	622165001	Paroxetine Tablets 20 mg “NP”	Paroxetine
SSRI	622166301	Paroxetine Tablets 10 mg “JG”	Paroxetine
SSRI	622166401	Paroxetine Tablets 20 mg “JG”	Paroxetine
SSRI	622168201	Paroxetine Tablets 5 mg “SAWAI”	Paroxetine
SSRI	622168301	Paroxetine Tablets 10 mg “SAWAI”	Paroxetine
SSRI	622168401	Paroxetine Tablets 20 mg “SAWAI”	Paroxetine
SSRI	622170701	Paroxetine Tablets 5 mg “DSEP”	Paroxetine
SSRI	622170801	Paroxetine Tablets 10 mg “DSEP”	Paroxetine
SSRI	622170901	Paroxetine Tablets 20 mg “DSEP”	Paroxetine
SSRI	622172801	Paroxetine Tablets 5 mg “Nichi-Iko”	Paroxetine
SSRI	622172901	Paroxetine Tablets 10 mg “Nichi-Iko”	Paroxetine
SSRI	622173001	Paroxetine Tablets 20 mg “Nichi-Iko”	Paroxetine
SSRI	622175101	Paroxetine Tablets 5 mg “DK”	Paroxetine
SSRI	622175201	Paroxetine Tablets 10 mg “DK”	Paroxetine
SSRI	622175301	Paroxetine Tablets 20 mg “DK”	Paroxetine
SSRI	622176601	Paroxetine Tablets 5 mg “SANDOZ”	Paroxetine
SSRI	622176701	Paroxetine Tablets 10 mg “SANDOZ”	Paroxetine
SSRI	622176801	Paroxetine Tablets 20 mg “SANDOZ”	Paroxetine
SSRI	622181001	Paroxetine Tablets 10 mg “KAKEN”	Paroxetine
SSRI	622181101	Paroxetine Tablets 20 mg “KAKEN”	Paroxetine
SSRI	622182201	Paroxetine Tablets 10 mg “KO”	Paroxetine
SSRI	622182301	Paroxetine Tablets 20 mg “KO”	Paroxetine
SSRI	622205201	Paroxetine Tablets 5 mg “JG”	Paroxetine
SSRI	622221201	Paroxetine Tablets 5 mg “KAKEN”	Paroxetine
SSRI	622234601	Paroxetine Tablets 5 mg “OHARA”	Paroxetine

SSRI	622236101	Paroxetine OD Tablets 5 mg “TOWA”	Paroxetine
SSRI	622249401	Paroxetine Tablets 5 mg “KN”	Paroxetine
SSRI	622253001	Paroxetine Tablets 5 mg “EE”	Paroxetine
SSRI	622262701	Paroxetine Tablets 5 mg “KO”	Paroxetine
SSRI	622283401	Paroxetine Tablets 5 mg “TEVA”	Paroxetine
SSRI	622283501	Paroxetine Tablets 10 mg “TEVA”	Paroxetine
SSRI	622283601	Paroxetine Tablets 20 mg “TEVA”	Paroxetine
SSRI	622473600	Paroxetine Hydrochloride 20 mg Tablets	Paroxetine
SSRI	622473700	Paroxetine Hydrochloride 5 mg Tablets	Paroxetine
SSRI	622488601	Paroxetine Tablets 5 mg “ASPEN”	Paroxetine
SSRI	622488701	Paroxetine Tablets 10 mg “ASPEN”	Paroxetine
SSRI	622488801	Paroxetine Tablets 20 mg “ASPEN”	Paroxetine
SSRI	622615500	Paroxetine Hydrochloride 10 mg Tablets	Paroxetine
SSRI	622659201	Paroxetine Tablets 5 mg “FELDSENF”	Paroxetine
SSRI	622659301	Paroxetine Tablets 10 mg “FELDSENF”	Paroxetine
SSRI	622659401	Paroxetine Tablets 20 mg “FELDSENF”	Paroxetine
SSRI	620003481	JZOLOFT Tablets 25 mg	Sertraline
SSRI	620003482	JZOLOFT Tablets 50 mg	Sertraline
SSRI	622356601	JZOLOFT Tablets 100 mg	Sertraline
SSRI	622366901	JZOLOFT OD Tablets 25 mg	Sertraline
SSRI	622367001	JZOLOFT OD Tablets 50 mg	Sertraline
SSRI	622367101	JZOLOFT OD Tablets 100 mg	Sertraline
SSRI	622442801	Sertraline Tablets 25 mg “KYORIN”	Sertraline
SSRI	622442901	Sertraline Tablets 50 mg “KYORIN”	Sertraline
SSRI	622443601	Sertraline Tablets 25 mg “YD”	Sertraline
SSRI	622443701	Sertraline Tablets 50 mg “YD”	Sertraline
SSRI	622445101	Sertraline Tablets 25 mg “Chemiphar”	Sertraline
SSRI	622445201	Sertraline Tablets 50 mg “Chemiphar”	Sertraline
SSRI	622446701	Sertraline Tablets 25 mg “TANABE”	Sertraline
SSRI	622446801	Sertraline Tablets 50 mg “TANABE”	Sertraline
SSRI	622448101	Sertraline Tablets 25 mg “TOWA”	Sertraline
SSRI	622448201	Sertraline Tablets 50 mg “TOWA”	Sertraline
SSRI	622449701	Sertraline Tablets 25 mg “TAKATA”	Sertraline
SSRI	622449801	Sertraline Tablets 50 mg “TAKATA”	Sertraline
SSRI	622449901	Sertraline Tablets 100 mg “TAKATA”	Sertraline

SSRI	622451601	Sertraline Tablets 25 mg “TCK”	Sertraline
SSRI	622451701	Sertraline Tablets 50 mg “TCK”	Sertraline
SSRI	622453501	Sertraline Tablets 25 mg “DSEP”	Sertraline
SSRI	622453601	Sertraline Tablets 50 mg “DSEP”	Sertraline
SSRI	622454601	Sertraline Tablets 25 mg “JG”	Sertraline
SSRI	622454701	Sertraline Tablets 50 mg “JG”	Sertraline
SSRI	622457501	Sertraline Tablets 25 mg “SAWAI”	Sertraline
SSRI	622457601	Sertraline Tablets 50 mg “SAWAI”	Sertraline
SSRI	622459601	Sertraline Tablets 25 mg “MEIJI”	Sertraline
SSRI	622459701	Sertraline Tablets 50 mg “MEIJI”	Sertraline
SSRI	622459801	Sertraline Tablets 100 mg “MEIJI”	Sertraline
SSRI	622459901	Sertraline Tablets 25 mg “SANDOZ”	Sertraline
SSRI	622460001	Sertraline Tablets 50 mg “SANDOZ”	Sertraline
SSRI	622463301	Sertraline Tablets 25 mg “AMEL”	Sertraline
SSRI	622463401	Sertraline Tablets 50 mg “AMEL”	Sertraline
SSRI	622463501	Sertraline Tablets 100 mg “AMEL”	Sertraline
SSRI	622463601	Sertraline OD Tablets 25 mg “AMEL”	Sertraline
SSRI	622463701	Sertraline OD Tablets 50 mg “AMEL”	Sertraline
SSRI	622463901	Sertraline Tablets 25 mg “SANWA”	Sertraline
SSRI	622464001	Sertraline Tablets 50 mg “SANWA”	Sertraline
SSRI	622464101	Sertraline Tablets 100 mg “SANWA”	Sertraline
SSRI	622466201	Sertraline Tablets 25 mg “Nichi-Iko”	Sertraline
SSRI	622466301	Sertraline Tablets 50 mg “Nichi-Iko”	Sertraline
SSRI	622467501	Sertraline Tablets 25 mg “TSURUHARA”	Sertraline
SSRI	622467601	Sertraline Tablets 50 mg “TSURUHARA”	Sertraline
SSRI	622467701	Sertraline Tablets 100 mg “TSURUHARA”	Sertraline
SSRI	622469001	Sertraline Tablets 25 mg “KAKEN”	Sertraline
SSRI	622469101	Sertraline Tablets 25 mg “NIPRO”	Sertraline
SSRI	622469201	Sertraline Tablets 50 mg “KAKEN”	Sertraline
SSRI	622469301	Sertraline Tablets 50 mg “NIPRO”	Sertraline
SSRI	622479401	Sertraline OD Tablets 25 mg “TOWA”	Sertraline
SSRI	622479501	Sertraline OD Tablets 50 mg “TOWA”	Sertraline
SSRI	622480601	Sertraline Tablets 100 mg “DSEP”	Sertraline
SSRI	622481601	Sertraline Tablets 100 mg “TCK”	Sertraline
SSRI	622481901	Sertraline Tablets 100 mg “Chemiphar”	Sertraline

SSRI	622484201	Sertraline Tablets 100 mg “KYORIN”	Sertraline
SSRI	622491301	Sertraline Tablets 100 mg “JG”	Sertraline
SSRI	622496401	Sertraline Tablets 100 mg “SANDOZ”	Sertraline
SSRI	622497701	Sertraline Tablets 100 mg “SAWAI”	Sertraline
SSRI	622504401	Sertraline Tablets 100 mg “TANABE”	Sertraline
SSRI	622505701	Sertraline Tablets 100 mg “KAKEN”	Sertraline
SSRI	622507001	Sertraline Tablets 100 mg “NIPRO”	Sertraline
SSRI	622510601	Sertraline Tablets 100 mg “YD”	Sertraline
SSRI	622513301	Sertraline OD Tablets 100 mg “TOWA”	Sertraline
SSRI	622513401	Sertraline Tablets 100 mg “TOWA”	Sertraline
SSRI	622528801	Sertraline Tablets 100 mg “Nichi-Iko”	Sertraline
SSRI	622610900	Sertraline Hydrochloride 25 mg Tablets (1)	Sertraline
SSRI	622611000	Sertraline Hydrochloride 50 mg Tablets (1)	Sertraline
SSRI	622611100	Sertraline Hydrochloride 100 mg Tablets	Sertraline
SSRI	622689800	Sertraline Hydrochloride 25 mg Tablets (2)	Sertraline
SSRI	622689900	Sertraline Hydrochloride 50 mg Tablets (2)	Sertraline
SSRI	622069502	LEXAPRO Tablets 10 mg	Escitalopram
SSRI	622675901	LEXAPRO Tablets 20 mg	Escitalopram
SNRI	620008497	Toledomin Tablets 12.5 mg	Milnacipran
SNRI	620008498	Toledomin Tablets 50 mg	Milnacipran
SNRI	620009123	Toledomin Tablets 15 mg	Milnacipran
SNRI	620009124	Toledomin Tablets 25 mg	Milnacipran
SNRI	620008086	Milnacipran Hydrochloride Tablets 15 mg “AMEL”	Milnacipran
SNRI	620008087	Milnacipran Hydrochloride Tablets 15 mg “AFP”	Milnacipran
SNRI	620008089	Milnacipran Hydrochloride Tablets 15 mg “NP”	Milnacipran
SNRI	620008090	Milnacipran Hydrochloride Tablets 15 mg “SAWAI”	Milnacipran
SNRI	620008091	Milnacipran Hydrochloride Tablets 15 mg “JG”	Milnacipran
SNRI	620008092	Milnacipran Hydrochloride Tablets 15 mg “TAIYO”	Milnacipran
SNRI	620008093	Milnacipran Hydrochloride Tablets 15 mg “TYK”	Milnacipran
SNRI	620008094	Milnacipran Hydrochloride Tablets 15 mg “TOWA”	Milnacipran
SNRI	620008095	Milnacipran Hydrochloride Tablets 15 mg “Nichi-Iko”	Milnacipran
SNRI	620008096	Milnacipran Hydrochloride Tablets 25 mg “AMEL”	Milnacipran
SNRI	620008097	Milnacipran Hydrochloride Tablets 25 mg “AFP”	Milnacipran
SNRI	620008099	Milnacipran Hydrochloride Tablets 25 mg “NP”	Milnacipran
SNRI	620008100	Milnacipran Hydrochloride Tablets 25 mg “SAWAI”	Milnacipran

SNRI	620008101	Milnacipran Hydrochloride Tablets 25 mg “JG”	Milnacipran
SNRI	620008102	Milnacipran Hydrochloride Tablets 25 mg “TAIYO”	Milnacipran
SNRI	620008103	Milnacipran Hydrochloride Tablets 25 mg “TYK”	Milnacipran
SNRI	620008104	Milnacipran Hydrochloride Tablets 25 mg “TOWA”	Milnacipran
SNRI	620008105	Milnacipran Hydrochloride Tablets 25 mg “Nichi-Iko”	Milnacipran
SNRI	621965101	Milnacipran Hydrochloride Tablets 50 mg “SAWAI”	Milnacipran
SNRI	621980301	Milnacipran Hydrochloride Tablets 12.5 mg “AMEL”	Milnacipran
SNRI	621980401	Milnacipran Hydrochloride Tablets 50 mg “AMEL”	Milnacipran
SNRI	621982501	Milnacipran Hydrochloride Tablets 50 mg “AFP”	Milnacipran
SNRI	621986801	Milnacipran Hydrochloride Tablets 12.5 mg “Nichi-Iko”	Milnacipran
SNRI	621986901	Milnacipran Hydrochloride Tablets 50 mg “Nichi-Iko”	Milnacipran
SNRI	621993401	Milnacipran Hydrochloride Tablets 12.5 mg “SAWAI”	Milnacipran
SNRI	621993501	Milnacipran Hydrochloride Tablets 50 mg “TYK”	Milnacipran
SNRI	622021601	Milnacipran Hydrochloride Tablets 12.5 mg “AFP”	Milnacipran
SNRI	622022601	Milnacipran Hydrochloride Tablets 12.5 mg “JG”	Milnacipran
SNRI	622029201	Milnacipran Hydrochloride Tablets 12.5 mg “TYK”	Milnacipran
SNRI	622055301	Milnacipran Hydrochloride Tablets 12.5 mg “TOWA”	Milnacipran
SNRI	622055401	Milnacipran Hydrochloride Tablets 50 mg “TOWA”	Milnacipran
SNRI	622058301	Milnacipran Hydrochloride Tablets 12.5 mg “TAIYO”	Milnacipran
SNRI	622058401	Milnacipran Hydrochloride Tablets 50 mg “TAIYO”	Milnacipran
SNRI	622070701	Milnacipran Hydrochloride Tablets 50 mg “JG”	Milnacipran
SNRI	622078701	Milnacipran Hydrochloride Tablets 12.5 mg “NP”	Milnacipran
SNRI	622078801	Milnacipran Hydrochloride Tablets 50 mg “NP”	Milnacipran
SNRI	621978201	Cymbalta Capsules 20 mg	Duloxetine
SNRI	621978301	Cymbalta Capsules 30 mg	Duloxetine
SNRI	622449501	EFFEXOR SR CAPSULES 37.5 mg	Venlafaxine
SNRI	622449601	EFFEXOR SR CAPSULES 75 mg	Venlafaxine
NaSSA	621932101	REFLEX TABLETS 15 mg	Mirtazapine
NaSSA	622497001	REFLEX TABLETS 30 mg	Mirtazapine
NaSSA	621929501	REMERON Tablets 15 mg	Mirtazapine
NaSSA	622482601	REMERON Tablets 30 mg	Mirtazapine
NaSSA	622647601	Mirtazapine Tablets 15 mg “Chemiphar”	Mirtazapine
NaSSA	622647701	Mirtazapine Tablets 30 mg “Chemiphar”	Mirtazapine
NaSSA	622648101	Mirtazapine Tablets 15 mg “YD”	Mirtazapine
NaSSA	622648201	Mirtazapine Tablets 30 mg “YD”	Mirtazapine

NaSSA	622648801	Mirtazapine Tablets 15 mg “Pfizer”	Mirtazapine
NaSSA	622648901	Mirtazapine Tablets 30 mg “Pfizer”	Mirtazapine
NaSSA	622650201	Mirtazapine OD Tablets 15 mg “DSEP”	Mirtazapine
NaSSA	622650301	Mirtazapine OD Tablets 30 mg “DSEP”	Mirtazapine
NaSSA	622650701	Mirtazapine Tablets 15 mg “TCK”	Mirtazapine
NaSSA	622650801	Mirtazapine Tablets 30 mg “TCK”	Mirtazapine
NaSSA	622652401	Mirtazapine Tablets 15 mg “EE”	Mirtazapine
NaSSA	622652501	Mirtazapine Tablets 15 mg “Nichi-Iko”	Mirtazapine
NaSSA	622652601	Mirtazapine Tablets 30 mg “EE”	Mirtazapine
NaSSA	622652701	Mirtazapine Tablets 30 mg “Nichi-Iko”	Mirtazapine
NaSSA	622654201	Mirtazapine OD Tablets 15 mg “AMEL”	Mirtazapine
NaSSA	622654301	Mirtazapine OD Tablets 30 mg “AMEL”	Mirtazapine
NaSSA	622655801	Mirtazapine OD Tablets 15 mg “SAWAI”	Mirtazapine
NaSSA	622655901	Mirtazapine OD Tablets 30 mg “SAWAI”	Mirtazapine
NaSSA	622656001	Mirtazapine Tablets 15 mg “SAWAI”	Mirtazapine
NaSSA	622656101	Mirtazapine Tablets 30 mg “SAWAI”	Mirtazapine
NaSSA	622657501	Mirtazapine Tablets 15 mg “TOWA”	Mirtazapine
NaSSA	622657601	Mirtazapine Tablets 30 mg “TOWA”	Mirtazapine
NaSSA	622657701	Mirtazapine OD Tablets 15 mg “TOWA”	Mirtazapine
NaSSA	622657801	Mirtazapine OD Tablets 30 mg “TOWA”	Mirtazapine
NaSSA	622658701	Mirtazapine Tablets 15 mg “NISSIN”	Mirtazapine
NaSSA	622658801	Mirtazapine Tablets 30 mg “NISSIN”	Mirtazapine
NaSSA	622659501	Mirtazapine Tablets 15 mg “FELDSENF”	Mirtazapine
NaSSA	622659601	Mirtazapine Tablets 30 mg “FELDSENF”	Mirtazapine
NaSSA	622660301	Mirtazapine Tablets 15 mg “KYOSOMIRAI”	Mirtazapine
NaSSA	622660401	Mirtazapine Tablets 30 mg “KYOSOMIRAI”	Mirtazapine
NaSSA	622661801	Mirtazapine Tablets 15 mg “KYORIN”	Mirtazapine
NaSSA	622661901	Mirtazapine Tablets 30 mg “KYORIN”	Mirtazapine
NaSSA	622662901	Mirtazapine Tablets 15 mg “TAKEDA TEVA”	Mirtazapine
NaSSA	622663001	Mirtazapine Tablets 30 mg “TAKEDA TEVA”	Mirtazapine
NaSSA	622663201	Mirtazapine Tablets 15 mg “AMEL”	Mirtazapine
NaSSA	622663301	Mirtazapine Tablets 30 mg “AMEL”	Mirtazapine
NaSSA	622664401	Mirtazapine Tablets 15 mg “JG”	Mirtazapine
NaSSA	622664501	Mirtazapine Tablets 30 mg “JG”	Mirtazapine
NaSSA	622666401	Mirtazapine OD Tablets 15 mg “NIPRO”	Mirtazapine

NaSSA	622666501	Mirtazapine OD Tablets 30 mg “NIPRO”	Mirtazapine
NaSSA	622666601	Mirtazapine Tablets 15 mg “NIPRO”	Mirtazapine
NaSSA	622666701	Mirtazapine Tablets 30 mg “NIPRO”	Mirtazapine
NaSSA	622667801	Mirtazapine Tablets 15 mg “MEIJI”	Mirtazapine
NaSSA	622667901	Mirtazapine Tablets 30 mg “MEIJI”	Mirtazapine
Other	622699301	Trintellix Tablets 10 mg	Vortioxetine
Other	622699401	Trintellix Tablets 20 mg	Vortioxetine