Report on the Deliberation Results

December 11, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Rexulti Tablets 1 mg Rexulti Tablets 2 mg Rexulti OD Tablets 0.5 mg Rexulti OD Tablets 1 mg Rexulti OD Tablets 2 mg
Non-proprietary Name	Brexpiprazole (JAN*)
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	January 30, 2023

Results of Deliberation

In its meeting held on December 8, 2023, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 28, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Rexulti Tablets 1 mg (b) Rexulti Tablets 2 mg (c) Rexulti OD Tablets 0.5 mg (d) Rexulti OD Tablets 1 mg (e) Rexulti OD Tablets 2 mg
Non-proprietary Name	Brexpiprazole
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	January 30, 2023
Dosage Form/Strength	(a) and (b) Film-coated tablets: Each tablet contains 1 or 2 mg of brexpiprazole. (c), (d), and (e) Orally disintegrating tablets: Each tablet contains 0.5, 1, or 2 mg of brexpiprazole.
Application Classification	Prescription drug, (4) Drugs with a new indication and (6) Drugs with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indications

Schizophrenia

Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy)

(Underline denotes additions.)

Dosage and Administration

Schizophrenia:

The usual initial adult dosage is 1 mg of brexpiprazole orally administered once daily for at least 4 days, and then the dose should be increased to 2 mg orally administered once daily.

Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy):

The usual adult dosage is 1 mg of brexpiprazole orally administered once daily. The dose may be increased to 2 mg/day only in patients who are tolerant of the current dose but have an inadequate response to it.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 25, 2023

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	(a) Rexulti Tablets 1 mg (b) Rexulti Tablets 2 mg (c) Rexulti OD Tablets 0.5 mg (d) Rexulti OD Tablets 1 mg (e) Rexulti OD Tablets 2 mg
Non-proprietary Name	Brexpiprazole
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	January 30, 2023
Dosage Form/Strength	(a) and (b) Film-coated tablets: Each tablet contains 1 or 2 mg of brexpiprazole. (c), (d), and (e) Orally disintegrating tablets: Each tablet contains 0.5, 1, or 2 mg of brexpiprazole.

Proposed Indications

Schizophrenia

Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy)

(Underline denotes additions.)

Proposed Dosage and Administration

Schizophrenia:

The usual initial adult dosage is 1 mg of brexpiprazole orally administered once daily for at least 4 days, and then the dose should be increased to 2 mg orally administered once daily.

Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy):

The usual adult dosage is 1 mg of brexpiprazole orally administered once daily. Then, the dose may be adjusted according to the patient's condition but should not exceed 2 mg/day. The dose may be increased only after at least 7 days of treatment at the current dose.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Brexpiprazole is an atypical antipsychotic discovered by Otsuka Pharmaceutical Co., Ltd. and acts as a partial agonist at serotonin 5-hydroxytryptamine (5-HT)$_{1A}$ and dopamine D_2 receptors and also as an antagonist at serotonin 5-HT$_{2A}$, adrenaline α_{1B}, and adrenaline α_{2C} receptors. In Japan, brexpiprazole was approved for the indication of schizophrenia in January 2018. Outside Japan, brexpiprazole was approved for the treatment of schizophrenia and the adjunctive treatment of major depressive disorder (MDD) in the US in 2015. As of September 2023, brexpiprazole is approved in at least 60 countries or regions including the US and Europe, and its use as an adjunctive therapy for MDD is approved in 25 countries or regions including the US.

In Japan, the applicant initiated a Japanese clinical study for the present application in July 2018. Based on results from the clinical study, the applicant submitted a partial change application for the extension of the indication of brexpiprazole to include an indication for the adjunctive treatment of depression and depressive state in patients who had an inadequate response to antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs).

2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no data relating to quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, data relating to primary pharmacodynamics have been submitted. Results from major studies are presented below.

3.1 Primary pharmacodynamics

3.1.1 *In vivo* studies

3.1.1.1 Forced swim test in rats (Reference CTD 4.2.1.1-01)

Rats orally received brexpiprazole 0.3, 1, or 3 mg/kg at 24 and 2 hours prior to the forced swim test. In this test, there was no difference in immobility time between any of the brexpiprazole groups and the vehicle[1)] group, indicating that brexpiprazole had no effect on immobility time.

Rats intraperitoneally received fluoxetine hydrochloride (fluoxetine) 16 or 32 mg/kg at 24, 4, and 1 hour prior to the forced swim test and also orally received brexpiprazole 0 or 3 mg/kg at 24 and 2 hours prior to the test. In this test, fluoxetine 32 mg/kg reduced immobility time compared with vehicle,[2)] and fluoxetine 32 mg/kg in combination with brexpiprazole reduced immobility time compared with fluoxetine 32 mg/kg alone. Concomitant brexpiprazole enhanced the effect of fluoxetine. Of note, there was no difference in immobility time between the fluoxetine 16 mg/kg group or fluoxetine 16 mg/kg + brexpiprazole group and the vehicle group, indicating that neither fluoxetine 16 mg/kg alone nor in combination with brexpiprazole had no effect on immobility time.

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1) 10% 2-hydroxypropyl-beta-cyclodextrine
2) Rats orally received 10% 2-hydroxypropyl-beta-cyclodextrine at 24 and 2 hours prior to the test and also intraperitoneally received 0.2% hydroxypropylmethylcellulose at 24, 4, and 1 hours prior to the test.

3.1.1.2 Study using chronic mild stress model in mice (Reference CTD 4.2.1.1-02)

Mice were continuously exposed to multiple types of mild stressors for 8 weeks. The animals were intraperitoneally received fluoxetine 5 or 10 mg/kg once daily in combination with brexpiprazole 0, 0.03, or 0.1 mg/kg twice daily orally for 5 weeks, beginning at 3 weeks after the start of the stress exposure. Behavioral parameters (coat state, nest building, splash test,[3)] novelty suppression of feeding test,[4)] cookie test,[5)] home-cage locomotor activity) were measured.

The coat state scores were continuously or transiently smaller in the fluoxetine 10 mg/kg + brexpiprazole 0.1 mg/kg and fluoxetine 10 mg/kg + brexpiprazole 0.03 mg/kg groups than in the fluoxetine 10 mg/kg group, indicating that concomitant brexpiprazole enhanced the effect of fluoxetine, but the enhanced effect was not observed in the fluoxetine 5 mg/kg + brexpiprazole 0.1 mg/kg group.

An increase in the nest building test score was noted only in the fluoxetine 10 mg/kg + brexpiprazole 0.1 mg/kg group compared with the vehicle group at 5 hours after placement of a nestlet in the cage, indicating that concomitant brexpiprazole enhanced the effect of fluoxetine, but at 24 hours after the placement, no such enhanced effect was noted in any group.

In either the splash test or novelty suppression of feeding test, concomitant brexpiprazole did not enhanced the effect of fluoxetine in any group.

In the cookie test, increases in the frequency of smelling the cookie and the number of cookie chews were noted only in the fluoxetine 10 mg/kg + brexpiprazole 0.1 mg/kg group compared with the fluoxetine 10 mg/kg group, indicating that concomitant brexpiprazole enhanced the effect of fluoxetine. However, no such enhanced effect in other measures was noted in any group.

An increase in the home-cage locomotor activity score was noted only in the fluoxetine 10 mg/kg + brexpiprazole 0.1 mg/kg group compared with the fluoxetine 10 mg/kg group, indicating that concomitant brexpiprazole enhanced the effect of fluoxetine.

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about the effect of brexpiprazole on the treatment of depression and depressive state:

The forced swim test in rats revealed that brexpiprazole alone did not have any effect, but the test suggested that brexpiprazole in combination with fluoxetine enhanced the effect of the co-administered drug. The study using the chronic mild stress model in mice showed that brexpiprazole enhanced the effect of fluoxetine on some of the measures.

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3) Mice were sprayed with 10% sucrose solution, and the latency to initiate the first grooming behavior as well as the frequency and duration of grooming were measured.

4) Latency to smell the food in a novel environment, frequency of smelling, time to start consuming the food, and food consumption were measured.

5) Latency to enter the grey chamber, latency to enter the dark chamber, latency to smell the cookie, frequency of smelling, latency to chew the cookie, and the number of cookie chews were measured.

The mechanism by which brexpiprazole acts to enhance the effect of the antidepressant remains unknown, but brexpiprazole's actions on relevant receptors may contribute to improvement in depression and depressive state in view of the following findings: (1) Brexpiprazole acts as a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors and also as an antagonist at serotonin 5-HT_{2A}, adrenaline α_{1B}, and adrenaline α_{2C} receptors (Review Report on "Rexulti Tablets 1 mg and others" dated November 16, 2017); and (2) a partial agonist at serotonin 5-HT_{1A} receptor (*Psychopharmacology. (Berl.)* 1990;101:497-504), an antagonist at serotonin 5-HT_{2A} receptor (*Synapse*. 2004;52:73-5), and an antagonist at adrenaline α_{2C} receptor (*Front Psychiatry.* 2017;8:144) reduced immobility time in the forced swim test, although brexpiprazole was not tested.

In addition, although the primary pharmacodynamics studies included in the submitted data all used fluoxetine, an SSRI, the enhanced antidepressant effect as observed with fluoxetine in combination with brexpiprazole in the primary pharmacodynamics studies can be expected for a combination of brexpiprazole and other existing antidepressants as well in view of the following reports: (i) Add-on brexpiprazole enhanced the effect of SSRIs including fluoxetine in the forced swim test in mice (*Neuropsychopharmacol Rep.* 2023;43:132-6); and (ii) SSRIs including fluoxetine, SNRIs, and mirtazapine are all thought to increase extracellular serotonin concentrations in the synaptic cleft, thereby exerting the antidepressant effect (*Folia Pharmacologica Japonica.* 2002;120:315-26, *J Clin Psychiatry.* 1996;57:19-25).

PMDA's view:
No *in vivo* study data submitted showed the effect of brexpiprazole alone. The forced swim test in rats revealed that fluoxetine in combination with brexpiprazole reduced immobility time compared with fluoxetine alone, indicating that brexpiprazole enhanced the effect of fluoxetine; and the chronic mild stress model study in mice revealed that concomitant brexpiprazole enhanced the effect of fluoxetine on some measures. The above findings suggest that brexpiprazole enhances the effect of fluoxetine.

Although the mechanism by which brexpiprazole acts to enhance the effect of the antidepressant remains unknown, the following applicant's explanation is understandable to a certain extent, in view of published literature presented by the applicant: Brexpiprazole's partial agonistic activities at serotonin 5-HT_{1A} and dopamine D_2 receptors as well as antagonistic activities at serotonin 5-HT_{2A}, adrenaline α_{1B}, and adrenaline α_{2C} receptors may contribute to the mechanism of action.

While fluoxetine was used in the studies included in the submitted data, antidepressants that are currently approved in Japan are SSRIs which are drugs in the same class as fluoxetine, SNRIs, and mirtazapine, and all of the drugs are considered to increase extracellular serotonin concentrations in the synaptic cleft, thereby exerting their effect. In view of these matters, the applicant's following explanation is also understandable to a certain extent: brexpiprazole can be expected to serve as an add-on therapy to not only fluoxetine but also other antidepressants approved in Japan.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new data have been submitted because the data on non-clinical pharmacokinetics had been evaluated during the review process for the initial approval of brexpiprazole.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no data on toxicity have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

For the present application, no data from biopharmaceutic studies have been submitted.

Plasma brexpiprazole concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation (LLOQ) = 0.3 ng/mL [0.5 ng/mL in the Japanese phase II/III study [Study 331-102-00058 or Study 00058]). Hereinafter, the dose of Rexulti is expressed as the amount of brexpiprazole.

6.2 Clinical pharmacology

6.2.1 Studies in patients with MDD

6.2.1.1 Ascending multiple-dose study in patients with MDD (Reference CTD 5.3.3.2-01, Study 331-09-221)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the safety, tolerability, and pharmacokinetics of ascending multiple doses of brexpiprazole in combination with an antidepressant in non-Japanese patients with MDD (17 patients evaluable for pharmacokinetic analysis). Patients orally received brexpiprazole at the specified doses (see Table 1) once daily (QD) for 18 days (2 days in the ascending-dose period (a), 2 days in the ascending-dose period (b), and 14 days in the fixed-dose period) in combination with SSRI or SNRI (Group 1 = escitalopram oxalate [escitalopram], sertraline hydrochloride [sertraline], desvenlafaxine succinate hydrate [desvenlafaxine], or venlafaxine hydrochloride [venlafaxine]; Group 2 = paroxetine hydrochloride hydrate [paroxetine] or fluoxetine).

Table 1 shows the pharmacokinetics parameters of plasma brexpiprazole on Day 14 of study treatment.

Table 1. Pharmacokinetics parameters of plasma brexpiprazole after multiple doses of brexpiprazole

Cohort/ group	Dose of brexpiprazole			No. of patients	Day 14			
	Ascending-dose period (a)	Ascending-dose period (b)	Fix-dose period		C_{max} (ng/mL)	t_{max}[a)] (h)	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (ng·h /mL)
1-1	1 mg	2 mg	3 mg	6	146 ± 44.2	3.00 [1.00, 3.00]	131 ± 66.2[b)]	2668 ± 993
1-2	0.5 mg	1 mg	1.5 mg	3	108 ± 75.2	1.00, 1.00[c)]	63.7[d)]	1899 ± 1378
2-1	2 mg	3 mg	4 mg	4	188 ± 66.3	2.53 [1.00, 3.00]	83.6 ± 22.2[b)]	3499 ± 1495
2-2	1 mg	1.5 mg	2 mg	4	125 ± 28.2	4.50 [1.00, 24.00]	76.4, 164[c)]	2406 ± 629

Mean ± standard deviation (SD), a) Median [minimum, maximum], b) n = 3, c) n = 2 (individual values), d) n = 1 (individual value)

6.2.1.2 Ascending multiple-dose study in elderly patients with MDD (Reference CTD 5.3.3.2-02, Study 331-12-291)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the safety, tolerability, and pharmacokinetics of ascending multiple doses of brexpiprazole in combination with an antidepressant in non-Japanese elderly patients with MDD aged ≥70 and ≤85 years (11 patients evaluable for pharmacokinetic analysis). In Cohort 1, patients orally received brexpiprazole 0.5 mg/day QD for 7 days, followed by 1 mg/day QD for 7 days during the ascending-dose period and then 2 mg/day QD for 14 days followed by 3 mg/day QD for 14 days during the fixed-dose period. In Cohort 2, patients orally received brexpiprazole as done in Cohort 1 during the ascending-dose period and then 3 mg/day QD for 14 days during the fixed-dose period. Cohort 3 (patients were to receive brexpiprazole 0.5 mg/day QD, 1 mg/day QD, and 2 mg/day QD for 7 days each during the ascending-dose period and then 3 mg/day QD for 14 days during the fixed-dose period) was planned but was omitted based on the results on the safety and tolerability of brexpiprazole in Cohorts 1 and 2.

In addition, use of potent cytochrome P-450 (CYP)2D6 inhibitors including paroxetine and fluoxetine was prohibited within 14 days before the first dose of brexpiprazole and throughout the study.

Table 2 shows plasma brexpiprazole concentrations at each sampling point on Day 14 of treatment with brexpiprazole at 3 mg/day during the fixed-dose period in Cohorts 1 and 2. These plasma brexpiprazole concentrations were 1.2 to 1.4 times higher than those on Day 14 of treatment with brexpiprazole at 3 mg/day in Group 1 of Cohort 1 in the study in non-elderly non-Japanese patients (aged ≥18 and ≤45 years) (Study 331-09-221).

Table 2. Plasma brexpiprazole concentrations at each sampling point on Day 14 of brexpiprazole multiple doses at 3 mg/day

Sampling point	No. of patients	Plasma brexpiprazole concentration (ng/mL)
Pre-dose	11	140 ± 53.4
2 hours post-dose	11	165 ± 69.5
6 hours post-dose	11	151 ± 60.1
12 hours post-dose	11	142 ± 62.3
24 hours post-dose	11	140 ± 58.7

Mean ± SD

6.2.1.3 Japanese phase II/III study in patients with MDD (CTD 5.3.5.1-01, Study 331-102-00058)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and pharmacokinetics of brexpiprazole in combination with an antidepressant (SSRI or SNRI) in Japanese patients with MDD (468 patients evaluable for pharmacokinetic analysis) [for the details of the study plan, see Section 7.2.1]. Subjects orally received placebo or brexpiprazole 1 or 2 mg/day QD in combination with an antidepressant (SSRI or SNRI) for 6 weeks during the double-blind period. In the 2 mg/day group, subjects started brexpiprazole at a dose of 1 mg/day and had the dose increased to 2 mg/day at Week 2.

Table 3 shows plasma brexpiprazole concentrations at each sampling point at Week 3 during the double-blind period.

Table 3. Plasma brexpiprazole concentrations in patients with MDD after administration of brexpiprazole 1 or 2 mg

	1 mg/day		2 mg/day	
Sampling point[a)]	No. of patients	Brexpiprazole concentration (ng/mL)	No. of patients	Brexpiprazole concentration (ng/mL)
0-6 hours post-dose	15	44.87 ± 26.13	17	72.41 ± 25.85
6-12 hours post-dose	28	35.23 ± 20.84	17	56.63 ± 25.27
12-18 hours post-dose	129	34.69 ± 21.34	126	67.63 ± 38.88
18-24 hours post-dose	34	31.45 ± 18.08	42	51.68 ± 32.20
24-30 hours post-dose	24	27.14 ± 12.90	24	55.84 ± 35.03
>30 hours post-dose	7	16.51 ± 15.81	5	48.91 ± 47.01

Mean ± SD, Values below the LLOQ were handled as zero (0).
a) Time after the last dose

6.2.1.4 Foreign phase III study in patients with MDD (CTD 5.3.5.1-02 and 5.3.5.1-03, Study 331-10-227)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and pharmacokinetics of brexpiprazole in combination with an antidepressant (SSRI or SNRI) in non-Japanese patients with MDD (414 patients evaluable for pharmacokinetic analysis). Subjects orally received placebo or brexpiprazole 1 or 3 mg/day QD for 6 weeks, in combination with an antidepressant (SSRI or SNRI), during the double-blind period. In the 1 mg/day group, subjects started brexpiprazole at a dose of 0.5 mg/day and had the dose increased to 1 mg/day at Week 2. In the 3 mg/day group, subjects started brexpiprazole 0.5 mg/day and had the dose increased to 1 mg/day at Week 2 and then 3 mg/day at Week 3.

Table 4 shows plasma brexpiprazole concentrations at Weeks 4, 5, and 6 during the double-blind period.

Table 4. Plasma brexpiprazole concentrations in patients with MDD receiving brexpiprazole 1 or 3 mg at Weeks 4, 5, and 6

	1 mg/day		3 mg/day	
Sampling point[a)]	No. of samples analyzed	Brexpiprazole concentration (ng/mL)	No. of samples analyzed	Brexpiprazole concentration (ng/mL)
0-6 hours post-dose	210	36.1 ± 19.4	217	118 ± 74.3
6-12 hours post-dose	53	39.6 ± 20.8	53	105 ± 60.6
12-18 hours post-dose	94	33.2 ± 17.8	93	93.8 ± 60.1
18-24 hours post-dose	72	31.3 ± 17.5	81	85.2 ± 62.8
24-30 hours post-dose	135	29.4 ± 20.1	105	78.7 ± 63.3
>30 hours post-dose	17	26.9 ± 22.5	21	46.6 ± 43.9

Mean ± SD, Values below the LLOQ were excluded.
Plasma brexpiprazole concentration data at Weeks 4, 5, and 6 were pooled.
a) Time after the last dose

6.2.1.5 Foreign phase III study in patients with MDD (CTD 5.3.5.1-02, Study 331-10-228)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and pharmacokinetics of brexpiprazole in combination with an antidepressant (SSRI or SNRI) in non-Japanese patients with MDD (165 patients evaluable for pharmacokinetic analysis). Subjects orally received placebo or brexpiprazole 2 mg/day QD for 6 weeks, in combination with an antidepressant (SSRI or SNRI), during the double-blind period. In the 2 mg/day group, subjects started brexpiprazole at a dose of 0.5 mg/day and had the dose increased to 1 mg/day at Week 2 and then 2 mg/day at Week 3.

Table 5 shows plasma brexpiprazole concentrations at Weeks 4, 5, and 6 during the double-blind period.

Table 5. Plasma brexpiprazole concentrations in patients with MDD receiving brexpiprazole 2 mg at Weeks 4, 5, and 6

Sampling point[a)]	No. of samples analyzed	Brexpiprazole concentration (ng/mL)
0-6 hours post-dose	179	77.1 ± 38.2
6-12 hours post-dose	67	74.2 ± 42.1
12-18 hours post-dose	46	61.4 ± 32.0
18-24 hours post-dose	51	56.3 ± 33.0
24-30 hours post-dose	82	50.3 ± 34.0
>30 hours post-dose	21	40.9 ± 28.6

Mean ± SD, Values below the LLOQ were excluded.
Plasma brexpiprazole concentration data at Weeks 4, 5, and 6 were pooled.
a) Time after the last dose

6.R Outline of the review conducted by PMDA

6.R.1 Necessity of dose adjustment of brexpiprazole for co-administration of potent CYP2D6 inhibitors

For the present application, the applicant proposed that in patients with depression or depressive state who had an inadequate response to existing antidepressant therapy, dose adjustment of brexpiprazole would not be needed when the drug is co-administered with a potent CYP2D6 inhibiting antidepressant, but the dose of brexpiprazole should be reduced when the drug is co-administered with any of potent CYP2D6 inhibitors that are not antidepressants.

PMDA asked the applicant to justify why dose adjustment of brexpiprazole is necessary when the drug is co-administered with potent CYP2D6 inhibitors.

The applicant's explanation:
In a drug-drug interaction study (Study 331-08-208), the co-administration of brexpiprazole with a potent CYP2D6 inhibitor (quinidine gluconate [quinidine]) increased brexpiprazole exposure (Review Report on "Rexulti Tablets 1 mg and others" dated November 16, 2017). The steady-state brexpiprazole exposure in patients receiving brexpiprazole in combination with paroxetine, a potent CYP2D6 inhibiting antidepressant, was estimated using a physiologically based pharmacokinetic (PBPK) model.[6)] The ratios of C_{max} and AUC values of brexpiprazole in patients receiving brexpiprazole in combination with paroxetine to those in patients receiving brexpiprazole alone were 1.16 and 2.25, respectively, suggesting that the combination of brexpiprazole and paroxetine increased brexpiprazole exposure, as with the combination of brexpiprazole and quinidine.

In view of the following findings, however, the applicant considers it appropriate to not adjust the dose of brexpiprazole for co-administration with the potent CYP2D6 inhibiting antidepressant (paroxetine): (1) In the Japanese clinical study (Study 00058), no safety concerns were noted in patients receiving brexpiprazole in combination with paroxetine, and the incidences and types of adverse events did not differ between these patients and those receiving brexpiprazole in combination with other antidepressants; and (2) in foreign clinical studies (Study 331-10-227 [Study 227] and Study 331-10-228 [Study 228]), no safety concerns that may require dose adjustment of brexpiprazole were

6) The Simcyp version 19 was applied to the PBPK model analysis.

noted in patients receiving concomitant paroxetine. Of note, Tables 6 to 8 show plasma brexpiprazole concentrations at each sampling point in patients receiving brexpiprazole with or without a potent CYP2D6 inhibiting antidepressant in the Japanese clinical study (Study 00058) and foreign clinical studies (Studies 227 and 228) where the dose of brexpiprazole was not adjusted for co-administration with a potent CYP2D6 inhibiting antidepressant (paroxetine or fluoxetine). At some sampling points, plasma brexpiprazole concentrations were higher in patients receiving brexpiprazole concomitantly with a potent CYP2D6 inhibiting antidepressant (paroxetine or fluoxetine) than in patients receiving brexpiprazole without antidepressants, but there was no consistent trend.

On the other hand, because the co-administration of brexpiprazole with other potent CYP2D6 inhibitors than paroxetine and fluoxetine was prohibited in Studies 00058, 227, and 228, the pharmacokinetics and safety of brexpiprazole in patients with depression or depressive state receiving brexpiprazole concomitantly with such CYP2D6 inhibitors have not been evaluated. Based on the results of the drug-drug interaction study of brexpiprazole with quinidine (Study 331-08-208) and PBPK model analysis, concomitant potent CYP2D6 inhibitors (such as quinidine) other than paroxetine and fluoxetine were presumed to increase brexpiprazole exposure to a similar extent to that observed with concomitant paroxetine. Co-administration of brexpiprazole with potent CYP2D6 inhibitors other than antidepressants without dose adjustment of brexpiprazole is unlikely to raise safety concerns. However, because of the limited experience with co-administration of brexpiprazole with potent CYP2D6 inhibitors, the mandatory dose adjustment should be appropriate.

Table 6. Plasma brexpiprazole concentrations (ng/mL) in patients with MDD receiving brexpiprazole 1 or 2 mg in Study 00058

Sampling point[a)]	1 mg/day		2 mg/day	
	With concomitant paroxetine	Without concomitant paroxetine	With concomitant paroxetine	Without concomitant paroxetine
0-6 hours post-dose	126 (1)[b)]	39.1 ± 13.9 (14)	69.9 (1)[b)]	72.6 ± 26.7 (16)
6-12 hours post-dose	57.1, 93.1 (2)[b)]	33.4 ± 17.0 (25)	-	60.2 ± 21.3 (16)
12-18 hours post-dose	58.8 ± 46.3 (6)	34.4 ± 18.4 (120)	92.4 ± 48.4 (7)	70.3 ± 35.2 (112)
18-24 hours post-dose	26.8 (1)[b)]	33.6 ± 17.0 (31)	32.8, 44.6 (2)[b)]	55.1 ± 31.3 (38)
24-30 hours post-dose	21.1 (1)[b)]	27.4 ± 13.1 (23)	-	60.9 ± 31.9 (22)
≥30 hours post-dose	-	23.1 ± 13.6 (5)	-	61.1 ± 44.2 (4)

Mean ± SD (number of patients evaluated); -, Not applicable; Values below the LLOQ were excluded.
a) Time after the last dose
b) Individual values (number of patients evaluated)

Table 7. Plasma brexpiprazole concentrations (ng/mL) in patients with MDD receiving brexpiprazole 1 or 3 mg in Study 227

Sampling point[a)]	1 mg/day			3 mg/day		
	With concomitant potent CYP2D6 inhibitors		Without concomitant potent CYP2D6 inhibitors	With concomitant potent CYP2D6 inhibitors		Without concomitant potent CYP2D6 inhibitors
	With concomitant paroxetine	With concomitant fluoxetine		With concomitant paroxetine	With concomitant fluoxetine	
0-6 hours post-dose	36.0 ± 15.5 (22)	41.6 ± 10.9 (10)	35.8 ± 20.3 (178)	188 ± 102 (11)	157 ± 103 (30)	107 ± 61.5 (176)
6-12 hours post-dose	39.6 ± 14.3 (6)	34.0 (1)[b)]	39.8 ± 21.8 (46)	109 ± 114 (7)	130 ± 53.8 (6)	100 ± 49.1 (40)
12-18 hours post-dose	33.7 ± 18.7 (20)	43.4 ± 14.9 (11)	31.3 ± 17.6 (63)	80.9 ± 96.0 (8)	99.2 ± 33.1 (8)	94.6 ± 58.3 (77)
18-24 hours post-dose	26.6 ± 12.2 (14)	58.4 ± 21. 4 (7)	28.8 ± 15.0 (51)	95.4 ± 65.1 (10)	95.8 ± 49.2 (9)	82.0 ± 64.7 (62)
24-30 hours post-dose	40.4 ± 27.3 (22)	17.5 ± 20.1 (6)	27.8 ± 17.6 (107)	93.3 ± 48.8 (18)	143 ± 72.6 (19)	56.7 ± 49.6 (68)
≥30 hours post-dose	70.8 (1)[b)]	45.0 (1) [b)]	22.7 ± 19.9 (15)	13.24, 32.7 (2)[b)]	37, 177 (2)[b)]	42.3 ± 39.4 (17)

Mean ± SD (number of samples evaluated), Values below the LLOQ were excluded.
Plasma brexpiprazole concentration data at Weeks 4, 5, and 6 were pooled.
a) Time after the last dose
b) Individual values (number of patients evaluated)

Table 8. Plasma brexpiprazole concentrations (ng/mL) in patients with MDD receiving brexpiprazole 2 mg in Study 228

Sampling point[a)]	2 mg/day		
	With concomitant potent CYP2D6 inhibitors		Without concomitant potent CYP2D6 inhibitors
	With concomitant paroxetine	With concomitant fluoxetine	
0-6 hours post-dose	91.8 ± 26.5 (13)	64.5 ± 30.8 (23)	77.8 ± 39.8 (143)
6-12 hours post-dose	79.4 ± 43.6 (16)	96.4 ± 27.2 (4)	70.5 ± 42.5 (47)
12-18 hours post-dose	62.9 ± 29.0 (12)	66.8 ± 18.5 (4)	60.0 ± 35.1 (30)
18-24 hours post-dose	43.4 ± 27.9 (8)	104 ± 88.3 (3)	55.3 ± 25.5 (40)
24-30 hours post-dose	85.6 ± 14.7 (10)	69.4 ± 42.0 (11)	41.1 ± 29.6 (61)
≥30 hours post-dose	59.6 ± 37.9 (4)	44.1 ± 26.2 (6)	32.4 ± 25.1 (11)

Mean ± SD (number of samples evaluated), Values below the LLOQ were excluded.
Plasma brexpiprazole concentration data at Weeks 4, 5, and 6 were pooled.
a) Time after the last dose

PMDA's view:

The following explanation provided by the applicant is acceptable: No dose reduction of brexpiprazole is needed when the drug is co-administered with paroxetine, a potent CYP2D6 inhibitor, because the Japanese and foreign clinical studies in patients with MDD have not raised safety concerns regarding the co-administration of brexpiprazole with the potent CYP2D6 inhibitor, paroxetine [see Section 7.R.3.6], although the drug-drug interaction study and these clinical studies indicated that concomitant potent CYP2D6 inhibitors increased brexpiprazole exposure.

Based on the results of the drug-drug interaction study and PBPK model analysis, use of concomitant potent CYP2D6 inhibitors other than paroxetine (such as quinidine and dacomitinib) was presumed to increase brexpiprazole exposure to a similar extent to that observed with concomitant paroxetine, which did not raise safety concerns. In view of this presumption, it is hardly necessary to reduce the dose of brexpiprazole to the extent of the increased exposure when the drug is co-administered with potent CYP2D6 inhibitors other than antidepressants. Furthermore, in any event, besides the co-administration of brexpiprazole with CYP2D6 inhibitors, where brexpiprazole exposure is assumed

to increase to an extent similar to that observed with concomitant paroxetine, it is hardly necessary to reduce the dose of brexpiprazole to the extent of the increased exposure.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from clinical studies, presented in Table 9.

Table 9. List of main clinical studies for efficacy and safety evaluation

Data category	Region	Study identifier CTD	Phase	Patient population	No. of enrolled patients	Dosage regimen	Main endpoints
Evaluation	Japan	Study 00058 5.3.5.1-01	II/III	Japanese patients with MDD who had an inadequate response to antidepressants	740	Placebo or brexpiprazole 1 or 2 mg/day orally for 6 weeks	Efficacy Safety Pharmacokinetics
		Study 00059 5.3.5.2-01	III (long-term)		248	Brexpiprazole 2 mg/day orally for 52 weeks	Safety Efficacy

7.1 Japanese phase II/III study (CTD 5.3.5.1-01, Study 00058, July 2018 to July 2022)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japan to evaluate the efficacy and safety of brexpiprazole co-administered with an antidepressant in patients with a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) who had an inadequate response to 8-week antidepressant monotherapy (target sample size, 720 patients; 240 per group[7)]).

The study was comprised of a screening period (up to 28 days), an antidepressant treatment period (8 weeks), a double-blind period (6 weeks), and a follow-up period (30 days, only for subjects who did not enter the Japanese long-term extension study [Study 331-102-00059 or Study 00059]) as well as an antidepressant-responder extension period (6 weeks).

The key inclusion criteria defined eligible patients as those aged ≥20 and <65 years who:

- Had a history of inadequate responses to 1 to 3 courses of adequate antidepressant treatment (at approved doses for at least 6 weeks) for the current episode of major depressive disorder at screening; AND
- Had a Hamilton Rating Scale for Depression (HAM-D)–17 Items (HAM-D17) total score ≥18 at screening and the start of the antidepressant treatment period.

Patients eligible for entering the double-blind period were those who had a HAM-D17 total score ≥14, showed a <50% reduction in HAM-D17 total score during the antidepressant treatment period, and had a Clinical Global Impression–Improvement (CGI-I) score of 3 (minimally improved) to 7 (very much worse) throughout the antidepressant treatment period.

7) The target sample size of 240 subjects per group was calculated on the assumption of a difference of −2.4 between the brexpiprazole and placebo groups for the primary endpoint, with a standard deviation of 7.7 to achieve 90% power at a two-sided significance level of 5%, including a dropout rate of 7%.

Antidepressant responders who were considered ineligible for entering the double-blind period at the end of the antidepressant treatment period (8 weeks) entered the antidepressant-responder extension period (6 weeks).

During the antidepressant treatment period, patients orally received an antidepressant, SSRI (fluvoxamine, paroxetine, sertraline, or escitalopram) or SNRI (milnacipran hydrochloride [milnacipran], duloxetine hydrochloride [duloxetine], or venlafaxine), which was different from prior antidepressants they had been taking at the time of informed consent, or placebo QD for 8 weeks in a single-blind design. The dose was up-titrated to the maximum approved dose wherever possible, and the same dosage regimen was maintained without any changes for the last 2 weeks. During the double-blind period, patients continued the single antidepressant (SSRI or SNRI) from the antidepressant treatment period at the last dosage regimen without any changes and also orally received placebo or brexpiprazole 1 or 2 mg/day QD for 6 weeks. In the 2 mg/day group, patients started brexpiprazole at a dose of 1 mg/day and had the dose increased to 2 mg/day at Week 2.

All of the 740 randomized subjects in the double-blind period (244 subjects in the placebo group, 250 subjects in the 1 mg/day group, and 246 subjects in the 2 mg/day group) were included in the safety analysis set, and 736 subjects (243 subjects, 248 subjects, and 245 subjects) who had the Montgomery Åsberg Depression Rating Scale (MADRS) total score measured at least once at baseline before the start of the double-blind period or later were included in the full analysis set (FAS) and the FAS was used for efficacy analysis. During the double-blind period, 51 subjects (12 subjects, 12 subjects, and 27 subjects) discontinued study treatment mainly because of adverse events in 24 subjects (3 subjects, 3 subjects, and 18 subjects), protocol deviation in 16 subjects (5 subjects, 3 subjects, and 8 subjects), consent withdrawal by subject in 7 subjects (1 subject, 5 subjects, and 1 subject), and remarkable non-compliance with the study drug in 1 subject (1 subject, 0 subject, and 0 subject).

Table 10 shows results on the primary endpoint, a change in MADRS total score from baseline (the end of the antidepressant treatment period) to the end of the double-blind period. Reductions in MADRS total score in the brexpiprazole 1 mg/day and 2 mg/day groups were greater than that in the placebo group with a statistical significance.

Table 10. Changes in MADRS total score from baseline to the end of the double-blind period (FAS)

Group		MADRS total score[a)]		Change[b) c)]	Difference from placebo [95% CI][c)]	*P* value[c) d)]
		Baseline	Final assessment			
Placebo		27.3 ± 6.2 (243)	20.5 ± 9.2 (233)	-6.7 ± 0.47		
Brexpiprazole	1 mg/day	26.7 ± 6.4 (248)	18.3 ± 8.8 (237)	-8.5 ± 0.47	-1.7 [-3.0, -0.4]	0.0089
	2 mg/day	26.9 ± 6.9 (245)	18.8 ± 9.0 (218)	-8.2 ± 0.47	-1.4 [-2.7, -0.1]	0.0312

a) Mean ± SD (number of patients evaluated)
b) Adjusted mean ± standard error (SE)
c) Analysis was performed by mixed-model repeated measures (MMRM) (with an unstructured correlation structure). The model included treatment group, timepoint, and interaction between the treatment group and timepoint as factors, and baseline MADRS total score and interaction between baseline MADRS total score and timepoint as covariates.
d) Two-sided significance level of 5%; multiplicity testing issue for comparisons between the placebo group and each of the brexpiprazole dose groups was taken into account using a fixed sequence procedure that applied to the 2 mg/day group and 1 mg/day group in this order.

Table 11 shows the summary of adverse events and the incidence of events reported by ≥2% of patients in any group in the overall population.

Table 11. Summary of adverse events and incidence of events reported by ≥2% of patients in any group in the overall population (safety analysis set)

	Placebo	Brexpiprazole	
		1 mg/day	2 mg/day
N	244	250	246
Any adverse event	144 (59.0)	155 (62.0)	182 (74.0)
Serious adverse events	2 (0.8)	3 (1.2)	3 (1.2)
Adverse events leading to treatment discontinuation	3 (1.2)	2 (0.8)	18 (7.3)
Adverse events reported by ≥2% of patients in any group			
Akathisia	3 (1.2)	15 (6.0)	60 (24.4)
Weight increased	6 (2.5)	18 (7.2)	19 (7.7)
Nasopharyngitis	24 (9.8)	20 (8.0)	16 (6.5)
Blood prolactin increased	6 (2.5)	6 (2.4)	15 (6.1)
Hyperprolactinaemia	3 (1.2)	3 (1.2)	13 (5.3)
Tremor	9 (3.7)	16 (6.4)	12 (4.9)
Insomnia	8 (3.3)	9 (3.6)	12 (4.9)
Extrapyramidal disorder	2 (0.8)	1 (0.4)	11 (4.5)
Constipation	5 (2.0)	5 (2.0)	9 (3.7)
Blood creatine phosphokinase increased	5 (2.0)	2 (0.8)	9 (3.7)
Hepatic function abnormal	6 (2.5)	3 (1.2)	8 (3.3)
Somnolence	6 (2.5)	3 (1.2)	8 (3.3)
Nausea	6 (2.5)	1 (0.4)	8 (3.3)
Alanine aminotransferase increased	4 (1.6)	8 (3.2)	7 (2.8)
Diarrhoea	7 (2.9)	6 (2.4)	7 (2.8)
Malaise	2 (0.8)	1 (0.4)	7 (2.8)
Hypertension	0	8 (3.2)	6 (2.4)
Blood insulin increased	1 (0.4)	5 (2.0)	6 (2.4)
Increased appetite	1 (0.4)	3 (1.2)	6 (2.4)
Salivary hypersecretion	1 (0.4)	2 (0.8)	6 (2.4)
Dizziness	6 (2.5)	4 (1.6)	5 (2.0)
Muscle rigidity	1 (0.4)	3 (1.2)	5 (2.0)
Back pain	4 (1.6)	2 (0.8)	5 (2.0)
Aspartate aminotransferase increased	3 (1.2)	6 (2.4)	4 (1.6)
Headache	11 (4.5)	6 (2.4)	3 (1.2)
Gamma-glutamyltransferase increased	3 (1.2)	6 (2.4)	3 (1.2)
Pyrexia	6 (2.5)	7 (2.8)	1 (0.4)

n (incidence [%])

No deaths occurred in any group. Serious adverse events other than deaths during the double-blind period occurred in 2 patients in the placebo group (cellulitis in 1 patient and subarachnoid haemorrhage in 1 patient), 3 patients in the 1 mg/day group (third cranial nerve paralysis in 1 patient, appendicitis in 1 patient, and intentional overdose in 1 patient), and 3 patients in the 2 mg/day group (epilepsy in 1 patient, alcoholic pancreatitis in 1 patient, and extramammary Paget's disease in 1 patient). A causal relationship to the study drug was ruled out for all events. Table 12 shows adverse events leading to discontinuation of study drug during the double-blind period.

Table 12. Adverse events leading to treatment discontinuation during the double-blind period (safety analysis set)

Placebo	Hepatic function abnormal in 1 patient, depression[a)] in 1 patient, and insomnia[a)] in 1 patient
1 mg/day	Dizziness,[a)] drooling,[a)] and hypoaesthesia[a)] in 1 patient; and mania[a)] in 1 patient
2 mg/day	Akathisia[a)] in 4 patients; malaise[a)] in 2 patients; dyspnea,[a)] dizziness,[a)] tinnitus,[a)] chills,[a)] akathisia,[a)] tremor,[a)] and malaise[a)] in 1 patient; major depression[a)] and extrapyramidal disorder[a)] in 1 patient; akathisia[a)] and mania[a)] in 1 patient; anxiety[a)] and restlessness[a)] in 1 patient; insomnia[a)] and paroxysmal perceptual alteration[a)] in 1 patient; periodontitis and dental caries in 1 patient; COVID-19 in 1 patient; tremor[a)] in 1 patient; muscle rigidity[a)] in 1 patient; extrapyramidal disorder[a)] in 1 patient; liver function test increased[a)] in 1 patient; and nausea in 1 patient

a) Event for which a causal relationship to the study drug cannot be ruled out

7.2 Japanese long-term extension study (CTD 5.3.5.2-01, Study 00059, October 2018 to April 2021)

An open-label uncontrolled study was conducted to investigate the long-term safety and efficacy of brexpiprazole in combination with an antidepressant in patients who completed the Japanese phase II/III study (Study 00058) (target sample size, 70 subjects) and newly enrolled patients (target sample size, 30 subjects).

The study consisted of a screening period (up to 28 days), a treatment period (52 weeks), and a follow-up period (30 days).

The key inclusion criteria for patients from Study 00058 defined eligible patients as those who had completed the double-blind period of Study 00058 and had a diagnosis of MDD according to the DSM-5.

Patients eligible to be newly enrolled in this study were defined as patients aged ≥65 years who had a diagnosis of MDD according to the DSM-5 and had a history of inadequate responses to 1 to 3 courses of adequate antidepressant treatment (at approved doses for at least 6 weeks) for the current episode of major depressive disorder.

Subjects started brexpiprazole at a dose of 1 mg/day and had the dose increased to 2 mg/day at Week 2. The oral QD regimen was continued for 52 weeks in total. The protocol allowed subjects who were intolerant of the treatment to discontinue the study without dose reduction or interruption. Patients from Study 00058 continued the concomitant antidepressant (SSRI or SNRI) at the last dosage regimen used in the previous study without any changes, and newly enrolled patients continued an antidepressant (SSRI, SNRI or mirtazapine) they had been taking before the start of the study at the dosage regimen used at the time of informed consent without any changes throughout the treatment period. Changes to the dose was allowed within the approved dose range on the discretion of the investigators, etc. during the study period, except at Week 2 when the dose of brexpiprazole was increased.

Of 248 patients who received brexpiprazole (216 patients from the previous study and 32 newly enrolled patients), 247 patients (216 patients and 31 patients) were included in the safety and efficacy analysis sets. The remaining 1 patient was excluded from the analyses because of a problem in the informed consent process. Of the patients who received brexpiprazole, 109 patients (84 patients and 25 patients) discontinued the study treatment mainly because of adverse events in 66 patients (48 patients and 18 patients), consent withdrawal by subject in 25 patients (20 patients and 5 patients), protocol deviation in 8 patients (8 patients and 0 patient), lack of efficacy in 4 patients (3 patients and 1 patient), and remarkable non-compliance with the study drug in 1 patient (1 patient and 0 patient).

Table 13 shows changes in MADRS total score from baseline (before the start of the treatment period) to each of assessment timepoints.

Table 13. Changes in MADRS total score from baseline (before start of brexpiprazole treatment) (efficacy analysis set)

	Baseline (before start of treatment)	Change from baseline (OC)				Change from baseline (LOCF)
		Week 8	Week 16	Week 24	Week 52	Week 52
Overall population	20.1 ± 8.9 (247)	-3.4 ± 6.8 (226)	-4.0 ± 7.4 (193)	-5.0 ± 8.2 (167)	-7.3 ± 8.7 (138)	-4.6 ± 9.2 (247)
Patients from the previous study	19.9 ± 8.8 (216)	-3.1 ± 6.5 (202)	-3.7 ± 7.2 (179)	-4.7 ± 8.0 (160)	-7.1 ± 8.7 (132)	-4.9 ± 9.0 (216)
Newly enrolled patients	22.2 ± 9.9 (31)	-5.8 ± 8.4 (24)	-7.4 ± 9.8 (14)	-11.6 ± 9.3 (7)	-11.2 ± 8.1 (6)	-2.8 ± 10.4 (31)

Mean ± SD (number of patients evaluated)
OC, Observed case; LOCF, Last observation carried forward

Table 14 shows the summary of adverse events and the incidence of events reported by ≥5% of patients in either population.

Table 14. Summary of adverse events and incidence of events reported by ≥5% of patients in either population (safety analysis set)

	Overall population	Patients from the previous study	Newly enrolled patients
N	247	216	31
Any adverse event	231 (93.5)	201 (93.1)	30 (96.8)
Serious adverse events	9 (3.6)	8 (3.7)	1 (3.2)
Adverse events leading to treatment discontinuation	66 (26.7)	48 (22.2)	18 (58.1)
Events reported by ≥5% of patients in either population			
Akathisia	58 (23.5)	46 (21.3)	12 (38.7)
Weight increased	82 (33.2)	78 (36.1)	4 (12.9)
Nasopharyngitis	52 (21.1)	47 (21.8)	5 (16.1)
Somnolence	26 (10.5)	24 (11.1)	2 (6.5)
Insomnia	24 (9.7)	22 (10.2)	2 (6.5)
Headache	23 (9.3)	22 (10.2)	1 (3.2)
Tremor	21 (8.5)	15 (6.9)	6 (19.4)
Increased appetite	18 (7.3)	17 (7.9)	1 (3.2)
Extrapyramidal disorder	16 (6.5)	12 (5.6)	4 (12.9)
Malaise	15 (6.1)	13 (6.0)	2 (6.5)
Major depression	14 (5.7)	10 (4.6)	4 (12.9)
Constipation	14 (5.7)	11 (5.1)	3 (9.7)
Diarrhoea	12 (4.9)	12 (5.6)	0
Nausea	12 (4.9)	12 (5.6)	0
Hyperprolactinaemia	11 (4.5)	11 (5.1)	0
Dyskinesia	11 (4.5)	7 (3.2)	4 (12.9)
Dizziness	11 (4.5)	9 (4.2)	2 (6.5)
Dystonia	8 (3.2)	5 (2.3)	3 (9.7)
Thirst	8 (3.2)	6 (2.8)	2 (6.5)
Fatigue	6 (2.4)	4 (1.9)	2 (6.5)
Bradykinesia	6 (2.4)	3 (1.4)	3 (9.7)
Hypertension	6 (2.4)	4 (1.9)	2 (6.5)
Palpitations	5 (2.0)	2 (0.9)	3 (9.7)
Parkinsonism	3 (1.2)	1 (0.5)	2 (6.5)

n (incidence [%])

One patient from the previous study died after discontinuation of the study drug. Although the cause of the death was not identified, a causal relationship to the study drug was ruled out. Serious adverse events other than death occurred in 7 patients from the previous study (duodenal perforation, septic shock, and arterial occlusive disease in 1 patient; appendicitis in 1 patient; HIV infection in 1 patient; ligament sprain in 1 patient; colon cancer, metastases to lymph nodes, and lung neoplasm malignant in 1 patient; dyskinesia in 1 patient; and depression in 1 patient) and 1 newly enrolled patient (major depression), and a causal relationship to the study drug was ruled out for all the events except dyskinesia and major depression. Table 15 shows adverse events leading to treatment discontinuation.

Table 15. Adverse events leading to treatment discontinuation (safety analysis set)

Newly enrolled patients	Akathisia[a)] in 4 patients; malaise[a)] in 2 patients; extrapyramidal disorder[a)] in 2 patients; fatigue[a)] and thirst[a)] in 1 patient; insomnia and dyskinesia[a)] in 1 patient; dystonia[a)] and parkinsonism[a)] in 1 patient; fatigue,[a)] disturbance in attention,[a)] increased appetite,[a)] and weight increased[a)] in 1 patient; major depression[a)] and akathisia[a)] in 1 patient; dizziness[a)] and akathisia[a)] in 1 patient; depression in 1 patient; hypertension[a)] in 1 patient; tremor[a)] in 1 patient; and major depression in 1 patient
Patients from the previous study	Weight increased[a)] in 4 patients; somnolence[a)] in 4 patients; extrapyramidal disorder[a)] in 2 patients; major depression in 2 patients; depression in 2 patients; anxiety[a)] in 2 patients; dyskinesia[a)] in 2 patients; malaise[a)] in 2 patients; akathisia[a)] in 2 patients; major depression[a)] in 1 patient; increased appetite[a)] and depression in 1 patient; dyskinesia[a)] and dystonia[a)] in 1 patient; malaise[a)] and increased appetite[a)] in 1 patient; weight increased[a)] and insomnia[a)] in 1 patient; anxiety, decreased appetite, and sleep disorder in 1 patient; akathisia[a)] and extrapyramidal disorder[a)] in 1 patient; photophobia[a)] and tremor[a)] in 1 patient; weight increased,[a)] somnolence,[a)] and feeling abnormal[a)] in 1 patient; insomnia[a)] and listless[a)] in 1 patient; duodenal perforation and arterial occlusive disease in 1 patient; bradykinesia[a)] and akathisia[a)] in 1 patient; oral discomfort[a)] in 1 patient; circadian rhythm sleep disorder in 1 patient; restless legs syndrome[a)] in 1 patient; dystonia[a)] in 1 patient; electrocardiogram QT prolonged[a)] in 1 patient; headache[a)] in 1 patient; syncope[a)] in 1 patient; head discomfort[a)] in 1 patient; HIV infection in 1 patient; colon cancer in 1 patient; anaemia in 1 patient; insomnia[a)] in 1 patient; attention deficit hyperactivity disorder in 1 patient; and increased appetite[a)] in 1 patient

a) Event for which a causal relationship to the study drug cannot be ruled out

7.R Outline of the review conducted by PMDA

7.R.1 Appropriateness of design of Japanese phase II/III study

7.R.1.1 Criteria for entering the double-blind period and evaluation period of the primary endpoint

PMDA asked the applicant to explain the appropriateness of the criteria for entering the double-blind period and of the evaluation period of the primary endpoint (corresponding to the double-blind period) in the Japanese phase II/III study (Study 00058).

The applicant's explanation:

- Study 00058 was designed with the intention of making brexpiprazole available for use in clinical practice as a drug for augmentation of antidepressants in patients who had an inadequate response to SSRI, SNRI, or mirtazapine, recommended as the first-line drugs by the guideline for treatment of depression used in Japan (Clinical Practice Guideline for the Treatment of Depression [in Japanese], version 2, Igaku-Shoin; 2017). In this study, as done in foreign phase III study (a) (Study 227), foreign phase III study (b) (Study 228), and foreign phase III study (c) (Reference, CTD 5.3.5.1-05, Study 331-13-214), subjects received an approved antidepressant or placebo in a single-blind manner during the antidepressant treatment period, and then subjects with an inadequate response to the antidepressant received placebo or brexpiprazole as add-on therapy to the antidepressant during the double-blind period.
- In Study 00058, an antidepressant treatment period of 8 weeks was selected because the period was considered long enough to evaluate a response to the antidepressant in accordance with the guideline for treatment of depression, and a double-blind period of 6 weeks was selected to evaluate the primary endpoint, as done in the foreign clinical studies.
- The criteria for entering the double-blind period in Study 00058 were defined as done in foreign clinical studies, and a Japanese phase III study of aripiprazole (Study 031-08-001) which is approved for augmentation of antidepressants in Japan was also referred to. Results from Study 031-08-001 suggested that some subjects with symptoms improved by the antidepressants entered the double-blind period because of transiently worsened symptoms at the end of the antidepressant

treatment period. In view of this finding, the applicant considered that only subjects with no clear improvement throughout the antidepressant treatment period, besides at the end of the period, should be eligible for entering the next period. Thus, the initial protocol of Study 00058 included the following criterion, and the protocols of Studies 227 and 228 were amended to include the criterion in the middle of the studies: Subjects with a CGI-I score of 3 (minimally improved) to 7 (very much worse) throughout the antidepressant treatment period are allowed to enter the double-blind period. In addition, to assess inadequate response to the antidepressants, the criteria for entering the double-blind period also included the following measures: <50% reduction in HAM-D17 total score and the HAM-D17 total score ≥14.

PMDA's view:
In the protocol of Study 00058, the CGI-I-based criterion for entering the double-blind period was specified to ascertain whether subjects were non-responders to the antidepressants throughout the antidepressant treatment period. The applicant considered that this criterion would ensure that only a population of patients eligible for treatment with brexpiprazole could be included in the double-blind period. In view of variations in the natural course of the symptoms in patients with depression, the applicant's decision is appropriate. The criteria based on the HAMD-17 total score also have no substantial problems.

In Study 00058, the 6-week double-blind period was selected to evaluate the primary endpoint. This length of the period is appropriate in view of changes over time in MADRS total score from baseline in the brexpiprazole and placebo groups in foreign clinical studies.

7.R.1.2 Dose of brexpiprazole in Japanese phase II/III study (Study 00058)

PMDA asked the applicant to explain the appropriateness of the dose of brexpiprazole in the Japanese phase II/III study (Study 00058).

The applicant's explanation:
Although there were no Japanese clinical studies of brexpiprazole in patients with MDD, no ethnic differences were observed in the pharmacokinetics of brexpiprazole. A dose of brexpiprazole to be used in Study 00058 was examined based on results from foreign clinical studies in patients with MDD. In the foreign phase III study (b) (Study 228) and foreign phase III study (c) (Study 331-13-214 [Study 214]), brexpiprazole 2 mg/day was demonstrated to be superior to placebo and confirmed to have acceptable safety and tolerability. The US labeling recommends 2 mg/day of brexpiprazole for "use as an adjunctive therapy for the treatment of major depressive disorder." In view of the above, the applicant selected brexpiprazole 2 mg/day as a dose in Study 00058, considering that it would be likely to be the optimal dose in Japanese patients with MDD, as with the US.

In the foreign phase III study (a) (Study 227), brexpiprazole 1 mg/day was not demonstrated to be superior to placebo in terms of a change in MADRS total score from baseline to Week 6, the primary endpoint, but the changes in MADRS total score in the 1 mg/day group at all the timepoints from Weeks 1 to 6 showed an improving trend compared with those in the placebo group. Taking account of the above results, 1 mg/day was also specified as another dose in Study 00058 to justify the dose in

Japanese patients with MDD. Based on the above considerations, Study 00058 was conducted as a randomized parallel-group study consisting of the 1 mg/day, 2 mg/day, and placebo groups.

Of note, the efficacy of brexpiprazole 3 mg/day was demonstrated in Study 227. The US labeling, however, refers to 3 mg/day only as the maximum dose but does not recommend it. According to the FDA integrated review report (https://www. accessdata.fda.gov/ drugsatfda_docs/nda/2015/205422Orig1Orig2s000 ClinPharmR. pdf [last accessed on October 11, 2023]), an exposure-response modeling analysis on pooled data from Studies 227 and 228 led to a statistical conclusion that the MADRS responder rate (proportion of subjects with ≥50% reduction in MADRS total score) did not significantly increase with an increase in the AUC of brexpiprazole. Results from foreign clinical studies revealed that the incidence of akathisia was dependent on the dose of brexpiprazole. In consideration of the above findings, Study 00058 did not include the 3 mg/day group.

PMDA's view:
Study 00058, which was conducted as a confirmatory study, included multiple brexpiprazole dose groups to find the recommended dose in Japanese patients. Such study design was unavoidable in view of the situation at the start of this study because no phase II study of brexpiprazole in patients with MDD was conducted in Japan. In addition, brexpiprazole 1 mg/day and 2 mg/day selected for Study 00058 are acceptable in view of the results from foreign clinical studies, which showed that the efficacy of brexpiprazole did not increase with an increase in the AUC of brexpiprazole; and the incidence of adverse events such as akathisia increased with the increasing dose of brexpiprazole.

7.R.2 Efficacy

The applicant's explanation about the efficacy of brexpiprazole in the treatment of depression and depressive state:
Results on the primary endpoint in the Japanese phase II/III study in Japanese patients with MDD (Study 00058) showed statistically significant reductions in both brexpiprazole 1 mg/day and 2 mg/day groups compared with the placebo group (Table 10). Table 16 shows changes over time in MADRS total score from baseline (the end of the antidepressant treatment period), indicating an improving trend in the brexpiprazole groups compared with the placebo group at all the timepoints at Week 2 onwards.

Table 16. Changes in MADRS total score from baseline to each timepoint of the double-blind period in Japanese phase II/III study (Study 00058) (FAS, MMRM)

Timepoint	Group	MADRS total score[a)]	Change from baseline[b)]	Difference from placebo [95% CI][c)]
Baseline	Placebo	27.3 ± 6.2 (243)	-	-
	1 mg/day	26.7 ± 6.4 (248)	-	-
	2 mg/day	26.9 ± 6.9 (245)	-	-
Week 1	Placebo	25.4 ± 7.0 (243)	-1.9 ± 0.27	-
	1 mg/day	24.4 ± 6.9 (248)	-2.4 ± 0.27	-0.4 [-1.2, 0.3]
	2 mg/day	24.3 ± 7.3 (244)	-2.6 ± 0.27	-0.7 [-1.4, 0.1]
Week 2	Placebo	24.5 ± 7.7 (233)	-2.9 ± 0.35	-
	1 mg/day	22.5 ± 7.7 (240)	-4.2 ± 0.35	-1.3 [-2.3, -0.4]
	2 mg/day	22.4 ± 7.8 (238)	-4.4 ± 0.35	-1.5 [-2.5, -0.6]
Week 3	Placebo	23.0 ± 8.1 (237)	-4.3 ± 0.39	-
	1 mg/day	20.9 ± 8.0 (237)	-5.9 ± 0.39	-1.6 [-2.7, -0.5]
	2 mg/day	20.9 ± 8.2 (231)	-6.2 ± 0.39	-1.9 [-3.0, -0.8]
Week 4	Placebo	21.9 ± 8.5 (232)	-5.2 ± 0.41	-
	1 mg/day	19.9 ± 8.4 (233)	-7.0 ± 0.41	-1.7 [-2.8, -0.6]
	2 mg/day	19.8 ± 8.4 (226)	-7.3 ± 0.41	-2.0 [-3.2, -0.9]
Week 5	Placebo	21.3 ± 8.8 (231)	-5.9 ± 0.44	-
	1 mg/day	19.3 ± 8.5 (233)	-7.6 ± 0.43	-1.7 [-2.9, -0.5]
	2 mg/day	19.6 ± 8.7 (223)	-7.4 ± 0.44	-1.5 [-2.7, -0.3]
Week 6	Placebo	20.5 ± 9.2 (233)	-6.7 ± 0.47	-
	1 mg/day	18.3 ± 8.8 (237)	-8.5 ± 0.47	-1.7 [-3.0, -0.4]
	2 mg/day	18.8 ± 9.0 (218)	-8.2 ± 0.47	-1.4 [-2.7, -0.1]

a) Mean ± SD (number of patients evaluated); -, Not calculated
b) Adjusted mean ± SE
c) Analysis was performed by MMRM (with an unstructured correlation structure). The model included treatment group, timepoint, and interaction between the treatment group and timepoint as factors, and baseline MADRS total score and interaction between baseline MADRS total score and timepoint as covariates.

In addition, the MADRS responder rate at the end of the double-blind period (proportion of patients with ≥50% reduction in MADRS total score from baseline [the end of the antidepressant treatment period]), the secondary endpoints, was 25.4% (63 of 248 patients) in the 1 mg/day group, 24.5% (60 of 245 patients) in the 2 mg/day group, and 18.9% (46 of 243 patients) in the placebo group, and the MADRS remission rate at that time (proportion of patients with a reduction in MADRS total score by ≥50% and to a score of ≤10) was 17.7% (44 of 248 patients) in the 1 mg/day group, 17.6% (43 of 245 patients) in the 2 mg/day group, and 13.6% (33 of 243 patients) in the placebo group.

Furthermore, a subgroup analysis by concomitant antidepressant was performed because brexpiprazole is administered as an add-on drug to antidepressants. Table 17 shows the results. Although the small sample size limits the interpretation of the data, the subgroup analysis did not suggest that the type of a concomitant antidepressant has any potential impact on the efficacy of brexpiprazole. Changes in MADRS total score in the brexpiprazole 2 mg/day + paroxetine subgroup, the brexpiprazole 1 mg/day + fluvoxamine subgroup, and the brexpiprazole 2 mg/day + fluvoxamine subgroup were smaller than that in the placebo group. These results are thought to be coincidental because of the small sample size, although the exact reason for this remains unknown. In a foreign long-term extension study (Study 16160A [CTD 5.3.5.2-03]) where use of concomitant mirtazapine was allowed, a change in MADRS total score from baseline to Week 26 (mean ± standard deviation [SD]) was −16.2 ± 7.8 in the overall population (89 patients) and −14.8 ± 7.6 in the concomitant mirtazapine subgroup (9 patients), showing no large difference.

As described above, the efficacy of brexpiprazole is unlikely to substantially differ depending on the type of a concomitant antidepressant (SSRI, SNRI, or mirtazapine), although the small sample size limits the interpretation of the data.

Subgroup analyses by patient characteristics (age, sex, number of depressive episodes, etc.) other than concomitant antidepressants were performed for Study 00058. The results of analyses did not identify any characteristics that might have a considerable impact on the efficacy of brexpiprazole.

Table 17. Changes in MADRS total score from baseline to the end of the double-blind period in Japanese phase II/III study (Study 00058) by concomitant antidepressant (FAS, MMRM)

Concomitant antidepressants	Group	MADRS total score[a)] (baseline)	Change from baseline[b)]	Difference from placebo [95% CI][c)]
Duloxetine	Placebo	27.6 ± 6.0 (39)	-7.4 ± 1.26	-
	1 mg/day	26.6 ± 7.0 (44)	-9.1 ± 1.18	-1.6 [-5.0, 1.8]
	2 mg/day	27.2 ± 6.3 (47)	-7.9 ± 1.15	-0.5 [-3.8, 2.9]
Escitalopram	Placebo	26.7 ± 5.8 (69)	-7.4 ± 0.91	-
	1 mg/day	27.4 ± 6.9 (81)	-8.1 ± 0.84	-0.7 [-3.2, 1.7]
	2 mg/day	26.1 ± 6.7 (77)	-8.0 ± 0.89	-0.6 [-3.1, 1.9]
Fluvoxamine	Placebo	26.8 ± 7.2 (10)	-10.0 ± 2.50	-
	1 mg/day	26.9 ± 8.3 (9)	-8.6 ± 2.76	1.3 [-6.4, 9.0]
	2 mg/day	29.1 ± 6.2 (9)	-3.1 ± 2.63	6.8 [-0.7, 14.4]
Milnacipran	Placebo	28.8 ± 6.5 (8)	-2.2 ± 2.98	-
	1 mg/day	28.6 ± 5.8 (5)	-5.7 ± 3.69	-3.5 [-13.4, 6.3]
	2 mg/day	19.0 ± 3.4 (5)	-11.2 ± 4.62	-9.0 [-21.6, 3.6]
Paroxetine	Placebo	27.7 ± 5.1 (15)	-7.2 ± 1.74	-
	1 mg/day	25.4 ± 6.5 (11)	-8.3 ± 2.03	-1.2 [-6.7, 4.3]
	2 mg/day	26.6 ± 6.1 (12)	-6.7 ± 1.93	0.5 [-4.8, 5.8]
Sertraline	Placebo	27.9 ± 6.4 (72)	-5.6 ± 0.76	-
	1 mg/day	26.6 ± 6.1 (77)	-8.0 ± 0.74	-2.4 [-4.5, -0.3]
	2 mg/day	26.2 ± 6.7 (77)	-8.5 ± 0.74	-2.9 [-5.0, -0.7]
Venlafaxine	Placebo	26.6 ± 7.1 (30)	-7.3 ± 1.46	-
	1 mg/day	24.5 ± 3.5 (21)	-10.0 ± 1.82	-2.7 [-7.2, 1.9]
	2 mg/day	34.1 ± 6.0 (18)	-10.4 ± 2.13	-3.1 [-8.4, 2.2]

a) Mean ± SD (number of patients evaluated); -, Not calculated
b) Adjusted mean ± SE
c) Analysis was performed by MMRM (with an unstructured correlation structure). The model included treatment group, timepoint, and interaction between the treatment group and timepoint as factors, and baseline MADRS total score and interaction between baseline MADRS total score and timepoint as covariates.

Table 13 shows changes over time in MADRS total score from baseline in Study 00059 where patients, including those from Study 00058, received brexpiprazole for 52 weeks, indicating that the efficacy of brexpiprazole co-administered with antidepressants for an extended period was maintained.

In the foreign phase III study (d) (CTD 5.3.5.1-06, Study 14570A), no statistically significant difference was observed in either primary or secondary endpoint between the brexpiprazole and placebo groups. PMDA asked the applicant to explain whether this result would deny the efficacy of brexpiprazole as a drug used for augmentation of antidepressants.

The applicant's explanation:
Study 14570A was comprised of the antidepressant treatment period (8 or 10 weeks) and double-blind period (24 weeks). The latter period included the group with a variable brexpiprazole dose of 1 to 3 mg/day (a constant dose was administered at Week 6 of the double-blind period and thereafter) and the placebo group. The study was designed and conducted for the primary endpoint of the proportion of patients who achieved complete remission (defined as patients with a MADRS total score of ≤10

for at least 8 consecutive weeks and ≥50% reduction in the MADRS total score from randomization) during the double-blind period. The result on the primary endpoint was 21.4% (95 of 444 patients) in the brexpiprazole group and 24.9% (110 of 441 patients) in the placebo group, with no statistically significant difference between the groups (odds ratio [95% confidence interval (CI)], 0.83 [0.60, 1.15]; $P = 0.2641$, a logistic regression model analysis using the MADRS total score at randomization as a covariate and treatment group, country, and allocation criteria[8)] as fixed effects). The result on one of the secondary endpoints, a change in MADRS total score from Weeks 0 to 6 of the double-blind period in the FAS (least mean square ± standard error [SE]) was −6.3 ± 0.4 in the brexpiprazole group and −5.9 ± 0.4 in the placebo group, with no difference between the groups (a difference between the groups [95% CI], −0.4 [−1.2, 0.4]; $P = 0.3259$; mixed-model repeated measures [MMRM] analysis [with an unstructured correlation structure] using treatment group, country, allocation criteria,[8)] timepoint, interaction between the allocation criteria[8)] and timepoint, interaction between the treatment group and timepoint as fixed effects and MADRS total score at randomization and interaction between the MADRS total score at randomization and timepoint as covariates).

On the other hand, in the foreign phase III studies (Studies 227, 228, 214, and 331-12-282 [CTD 5.3.5.1-04]), which were conducted in a design similar to that of the Japanese phase II/III study (Study 00058), a statistically significant difference was observed in a change in MADRS total score from baseline to the end of the double-blind period (6 weeks), the primary endpoint, when any of the 3 mg/day group in Study 227, 2 mg/day group in Studies 228 and 214 as well as brexpiprazole variable dose (2 or 3 mg/day) group in Study 282 was compared with the corresponding placebo group.

Study 14570A and the other clinical studies (Studies 00058, 227, 228, 214, and 282) differed in terms of duration of the study treatment in the double-blind period and efficacy evaluation timepoints (6 or 24 weeks) and the primary endpoint (proportion of patients with complete remission based on the change in MADRS total score or the MADRS total score). The long-term treatment with brexpiprazole was not considered responsible for the observed lack of the efficacy in Study 14570A because the change in MADRS total score from the start of the double-blind period to Week 6, one of the secondary endpoints in Study 14570A, did not show any difference between the brexpiprazole and placebo groups. The characteristics of the patients enrolled did not substantially differ among the studies, and thus the reason for the observed lack of the significant difference between the brexpiprazole and placebo groups remained unknown. However, of 81 randomized double-blind studies conducted during the development of antidepressants submitted to FDA between 1983 and 2008, 43 studies (53%) demonstrated the efficacy (*J Clin Psychiatry.* 2011;72:464-72). The applicant considers it generally difficult to demonstrate the superiority of an investigational antidepressant to placebo in a clinical study. In light of this result, the effect of brexpiprazole as a drug used for augmentation of antidepressants is not denied solely by the finding from Study 14570A because multiple clinical studies have demonstrated the efficacy of brexpiprazole versus placebo.

8) Factor that reflects differences in timepoint of the patient's entering the double-blind period and criteria for entering this period

PMDA's view:
In the Japanese phase II/III study (Study 00058), a change in MADRS total score from baseline (the end of the antidepressant treatment period) to the end of the double-blind period (6 weeks), the primary endpoint, demonstrated the superiority of brexpiprazole to placebo, and the MADRS responder rate and MADRS remission rate during the double-blind period, the secondary endpoints, in both brexpiprazole groups were higher than those in the placebo group, showing an improving trend. The efficacy of brexpiprazole did not tend to differ depending on the type of concomitant antidepressants (including paroxetine, known as a potent CYP2D6 inhibitor) in Study 00058 and other studies. Furthermore, in the Japanese long-term extension study (Study 00059), the efficacy of brexpiprazole tended to be maintained to a certain extent during the treatment.

In contrast, the foreign clinical study (Study 14570A), which assessed the efficacy of brexpiprazole versus placebo at Week 24, failed to demonstrate the superiority of brexpiprazole to placebo, although other clinical studies conducted in and outside Japan demonstrated the efficacy of brexpiprazole. Changes over time in MADRS total score from baseline, the secondary endpoint in Study 14570A, did not show a clear difference between the brexpiprazole and placebo groups even at Week 6, and thus the long-term treatment with brexpiprazole was not responsible for the observed lack of the efficacy of brexpiprazole in this study. The applicant's discussion could not identify a reason for the observed lack of efficacy. However, Study 00058 and multiple foreign phase III studies (Studies 227, 228, 214, and 282) have demonstrated the superiority of brexpiprazole to placebo. In view of this fact and other data, the efficacy of brexpiprazole cannot be denied solely based on the results of Study 14570A.

Based on the above, PMDA has concluded that the Japanese clinical studies (Studies 00058 and 00059) have demonstrated the efficacy of brexpiprazole co-administered with antidepressants in Japanese patients with depression or depressive state.

7.R.3 Safety

As a result of the following review in Sections 7.R.3.1 to 7.R.3.6 on the basis of the submitted study results, PMDA has concluded that brexpiprazole has the acceptable safety in Japanese patients with depression or depressive state in view of the observed efficacy [see Section 7.R.2]; provided that appropriate precautions should be exercised to carefully monitor the occurrence of adverse events including extrapyramidal symptoms such as akathisia, weight increased, and suicide-related and hostility/aggression-related adverse events in patients receiving brexpiprazole.

7.R.3.1 Safety profile of brexpiprazole in patients with MDD

PMDA asked the applicant to explain the safety profile of brexpiprazole in patients with MDD in comparison with that in patients with schizophrenia.

The applicant's explanation:
Table 18 shows the incidences of major adverse events in the Japanese clinical studies (Studies 00058 and 331-10-002 in the initial application [CTD 5.3.5.1-01]) where patients with MDD or schizophrenia received brexpiprazole or placebo for 6 weeks. The incidences of any adverse event did not substantially differ between the diseases, and both incidences of serious adverse events and

adverse events leading to treatment discontinuation tended to be lower in patients with MDD than in patients with schizophrenia. Of events reported by ≥2% of patients in any group in Study 00058 in patients with MDD, only akathisia and weight increased occurred at an incidence that was ≥5% higher in patients with MDD than in patients with schizophrenia. Thus, there were no additional events requiring caution for use in patients with MDD.

Table 18. Incidences of major adverse events in Japanese clinical studies in patients with MDD or schizophrenia (safety analysis set)

	Study in patients with MDD (Study 00058)			Study in patients with schizophrenia (Study 331-10-002 in the initial application [CTD 5.3.5.1-01])			
	Placebo	Brexpiprazole		Placebo	Brexpiprazole		
		1 mg/day	2 mg/day		1 mg/day	2 mg/day	4 mg/day
Treatment duration	6 weeks						
N	244	250	246	116	115	114	113
Any adverse event	144 (59.0)	155 (62.0)	182 (74.0)	89 (76.7)	81 (70.4)	79 (69.3)	74 (65.5)
Serious adverse events	2 (0.8)	3 (1.2)	3 (1.2)	5 (4.3)	8 (7.0)	5 (4.4)	5 (4.4)
Adverse events leading to treatment discontinuation	3 (1.2)	2 (0.8)	18 (7.3)	20 (17.2)	19 (16.5)	12 (10.5)	17 (15.0)
Adverse events reported by ≥2% of patients in any group in Study 00058							
Akathisia	3 (1.2)	15 (6.0)	60 (24.4)	8 (6.9)	2 (1.7)	4 (3.5)	6 (5.3)
Weight increased	6 (2.5)	18 (7.2)	19 (7.7)	0	0	1 (0.9)	0
Nasopharyngitis	24 (9.8)	20 (8.0)	16 (6.5)	11 (9.5)	12 (10.4)	8 (7.0)	10 (8.8)
Blood prolactin increased	6 (2.5)	6 (2.4)	15 (6.1)	3 (2.6)	1 (0.9)	3 (2.6)	7 (6.2)
Hyperprolactinaemia	3 (1.2)	3 (1.2)	13 (5.3)	1 (0.9)	0	0	1 (0.9)
Tremor	9 (3.7)	16 (6.4)	12 (4.9)	3 (2.6)	3 (2.6)	3 (2.6)	1 (0.9)
Insomnia	8 (3.3)	9 (3.6)	12 (4.9)	3 (2.6)	3 (2.6)	1 (0.9)	3 (2.7)
Extrapyramidal disorder	2 (0.8)	1 (0.4)	11 (4.5)	2 (1.7)	1 (0.9)	2 (1.8)	4 (3.5)
Constipation	5 (2.0)	5 (2.0)	9 (3.7)	9 (7.8)	8 (7.0)	8 (7.0)	7 (6.2)
Blood creatine phosphokinase increased	5 (2.0)	2 (0.8)	9 (3.7)	2 (1.7)	3 (2.6)	2 (1.8)	2 (1.8)
Hepatic function abnormal	6 (2.5)	3 (1.2)	8 (3.3)	2 (1.7)	0	1 (0.9)	0
Somnolence	6 (2.5)	3 (1.2)	8 (3.3)	1 (0.9)	2 (1.7)	3 (2.6)	0
Nausea	6 (2.5)	1 (0.4)	8 (3.3)	2 (1.7)	4 (3.5)	6 (5.3)	3 (2.7)
Alanine aminotransferase increased	4 (1.6)	8 (3.2)	7 (2.8)	1 (0.9)	1 (0.9)	1 (0.9)	2 (1.8)
Diarrhoea	7 (2.9)	6 (2.4)	7 (2.8)	2 (1.7)	4 (3.5)	3 (2.6)	6 (5.3)
Malaise	2 (0.8)	1 (0.4)	7 (2.8)	1 (0.9)	1 (0.9)	2 (1.8)	2 (1.8)
Hypertension	0	8 (3.2)	6 (2.4)	1 (0.9)	0	0	1 (0.9)
Blood insulin increased	1 (0.4)	5 (2.0)	6 (2.4)	1 (0.9)	2 (1.7)	1 (0.9)	0
Increased appetite	1 (0.4)	3 (1.2)	6 (2.4)	0	0	0	0
Salivary hypersecretion	1 (0.4)	2 (0.8)	6 (2.4)	0	1 (0.9)	3 (2.6)	1 (0.9)
Dizziness	6 (2.5)	4 (1.6)	5 (2.0)	1 (0.9)	0	5 (4.4)	3 (2.7)
Muscle rigidity	1 (0.4)	3 (1.2)	5 (2.0)	0	2 (1.7)	0	0
Back pain	4 (1.6)	2 (0.8)	5 (2.0)	1 (0.9)	3 (2.6)	2 (1.8)	3 (2.7)
Aspartate aminotransferase increased	3 (1.2)	6 (2.4)	4 (1.6)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Headache	11 (4.5)	6 (2.4)	3 (1.2)	5 (4.3)	8 (7.0)	9 (7.9)	3 (2.7)
Gamma-glutamyltransferase increased	3 (1.2)	6 (2.4)	3 (1.2)	1 (0.9)	0	1 (0.9)	0
Pyrexia	6 (2.5)	7 (2.8)	1 (0.4)	3 (2.6)	2 (1.7)	2 (1.8)	3 (2.7)

n (incidence [%])

The long-term safety of brexpiprazole was assessed. The incidences of total adverse events in Japanese long-term extension studies in patients with MDD and patients with schizophrenia (Study 00059 and Study 331-10-003 in the initial application [CTD 5.3.5.2-01]) were 93.5% (231 of 247 patients) and 83.6% (235 of 281 patients), respectively; the incidences of serious adverse events were 3.6% (9 of 247 patients) and 13.2% (37 of 281 patients), respectively; and the incidences of adverse events leading to treatment discontinuation were 26.7% (66 of 247 patients) and 15.3% (43 of 281 patients), respectively. The incidence of adverse events leading to treatment discontinuation tended to be higher in patients with MDD than in patients with schizophrenia. However, the long-term extension study in patients with schizophrenia allowed the dose reduction of brexpiprazole, and thus the incidence of adverse events leading to treatment discontinuation or dose reduction in this patient population

(35.2%) should be used in this comparison; the incidence of adverse events leading to treatment discontinuation in patients with MDD tended to be lower than 35.2%. Of adverse events reported by ≥10% of patients with MDD in the brexpiprazole group, events of which the incidence was ≥5% higher in patients with MDD than in patients with schizophrenia were only weight increased and akathisia.

The safety in the elderly (≥65 years) was assessed. The incidence of adverse events in Study 00059 was 93.1% (201 of 216 patients) in patients from Study 00058 (non-elderly) and 96.8% (30 of 31 patients) in newly enrolled patients (elderly), with no difference between the subgroups. The interpretation of the data, however, has limitations because of different treatment durations. The incidence of serious adverse events (including deaths) in Study 00059 was 3.7% (8 of 216 patients) in the non-elderly and 3.2% (1 of 31 patients) in the elderly, while that of adverse events leading to discontinuation of brexpiprazole was 22.2% (48 of 216 patients) in the non-elderly and 58.1% (18 of 31 patients) in the elderly. Such adverse events tended to be more common in the elderly than in the non-elderly, and this was probably because akathisia frequently occurred in the elderly (Table 19).

In view of the above findings, the applicant considers that the incidences of adverse events differ between patients with MDD and patients with schizophrenia, but there are no substantial differences in the types of events between these patient populations.

PMDA's view:
In view of adverse events reported in clinical studies and the pharmacological action of brexpiprazole, extrapyramidal symptoms-related adverse events including akathisia, weight increased, convulsion- and oversedation-related adverse events, suicide and hostility/aggression-related adverse events that may occur in patients being treated with brexpiprazole, and the safety of brexpiprazole by concomitant antidepressant are reviewed in detail in Section 7.R.3.2 and subsequent sections [see Sections 7.R.3.2 to 7.R.3.6]. Adverse events other than the above events in patients being treated with brexpiprazole raise no serious concerns about the use of brexpiprazole in clinical settings, in light of their incidence and severity in clinical studies.

7.R.3.2 Extrapyramidal symptoms

Since extrapyramidal symptoms are known to occur with antipsychotics, PMDA asked the applicant to explain about the relevant events reported in patients being treated with brexpiprazole.

The applicant's explanation:
Table 19 shows the incidences of extrapyramidal symptoms-related adverse events[9)] in the Japanese phase II/III study (Study 00058) and Japanese long-term extension study (Study 00059). Extrapyramidal symptoms-related adverse events more frequently occurred in the brexpiprazole groups than in the placebo group in a dose-dependent manner, but most of them were mild to moderate.

9) Events coded to "Extrapyramidal syndrome" (narrow or broad), a Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) and events listed below.
Clumsiness, fumbling, nuchal rigidity, myotonia, asterixis, essential tremor, intention tremor, myoclonus, dysarthria, dyslalia, tongue paralysis, gaze palsy, glabellar reflex abnormal, restless legs syndrome, muscle contracture, periodic limb movement disorder, excessive eye blinking, salivary hypersecretion, Huntington's disease, saliva altered, and head titubation

Table 19. Extrapyramidal symptoms-related adverse events (Studies 00058 and 00059, safety analysis set)

	Study 00058			Study 00059		
				2 mg/day		
	Placebo	1 mg/day	2 mg/day	Overall population	Patients from the previous study	Newly enrolled patients
N	244	250	246	247	216	31
Extrapyramidal symptoms-related adverse events	18 (7.4)	37 (14.8)	90 (36.6)	98 (39.7)	76 (35.2)	22 (71.0)
Serious adverse events	0	0	0	1 (0.4)	1 (0.4)	0
Adverse events leading to treatment discontinuation	0	1 (0.4)	12 (4.9)	27 (10.9)	15 (6.9)	12 (38.7)
Adverse events reported by ≥2% of patients in any group						
Akathisia	3 (1.2)	15 (6.0)	60 (24.4)	58 (23.5)	46 (21.3)	12 (38.7)
Tremor	9 (3.7)	16 (6.4)	12 (4.9)	21 (8.5)	15 (6.9)	6 (19.4)
Extrapyramidal disorder	2 (0.8)	1 (0.4)	11 (4.5)	16 (6.5)	12 (5.6)	4 (12.9)
Dyskinesia	0	3 (1.2)	3 (1.2)	11 (4.5)	7 (3.2)	4 (12.9)
Parkinsonism	0	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.5)	2 (6.5)
Salivary hypersecretion	1 (0.4)	2 (0.8)	6 (2.4)	5 (2.0)	4 (1.9)	1 (3.2)
Muscle rigidity	1 (0.4)	3 (1.2)	5 (2.0)	1 (0.4)	1 (0.5)	0
Dystonia	1 (0.4)	3 (1.2)	1 (0.4)	8 (3.2)	5 (2.3)	3 (9.7)
Bradykinesia	0	2 (0.8)	3 (1.2)	6 (2.4)	3 (1.4)	3 (9.7)
Gait disturbance	0	0	2 (0.8)	1 (0.4)	0	1 (3.2)

n (incidence [%])

While no serious adverse events occurred in Study 00058, serious dyskinesia occurred in 1 patient in Study 00059. The event was considered causally related to the study drug but moderate in severity and resolved after discontinuation of brexpiprazole. An analysis on pooed data from foreign clinical studies[10)] revealed no serious adverse events, but an analysis on integrated data from foreign long-term extension studies[11)] identified serious extrapyramidal disorder in 1 patient. The event was considered causally related to the study drug but resolved after discontinuation of brexpiprazole.

The use of concomitant anticholinergic antiparkinson drugs was allowed for the treatment of extrapyramidal symptoms. Such drugs were used in 4.4% (11 of 250) of patients in the 1 mg/day group, 19.9% (49 of 246) of patients in the 2 mg/day group, and 1.2% (3 of 244) of patients in the placebo group in Study 00058, and also used in 21.9% (54 of 247) of overall study patients and 19.4% (6 of 31) of newly enrolled patients (the elderly aged ≥65 years) in Study 00059. For the entire population receiving brexpiprazole, the incidence of extrapyramidal symptoms-related adverse events (including worsening) after the co-administration of anticholinergic antiparkinson drugs with brexpiprazole was 13.3% (8 of 60 patients) in Study 00058 and 25.9% (14 of 54 patients) in Study 00059.

Akathisia, the most common event in this category, occurred more frequently in both brexpiprazole dose groups than in the placebo group in Study 00058, and the event tended to more frequently occur in the 2 mg/day group than in the 1 mg/day group (Table 19). Most of the events of akathisia reported in the brexpiprazole dose groups were mild to moderate, and none of them were considered serious. The events leading to treatment discontinuation occurred in 6 patients (2.4%) who were all in the

10) Study 331-08-211 (Reference, CTD 5.3.5.1-07), Study 331-09-222 (Reference, CTD 5.3.5.2-08), Study 331-10-227 (Reference, CTD 5.3.5.1-02), Study 331-10-228 (Reference, CTD 5.3.5.1-03), Study 331-12-282 (Reference, CTD 5.3.5.1-04), Study 331-13-214 (Reference, 5.3.5.1-05)

11) Study 331-08-212 (Reference, CTD 5.3.5.2-04), Study 331-10-238 (Reference, CTD 5.3.5.2-02)

2 mg/day group. The events were confirmed to have resolved or be resolving after the treatment discontinuation. According to an analysis in the overall population of Study 00059, akathisia occurred in 58 of 247 patients (23.5%). Of the patients, 4 from the previous study (non-elderly) and 6 new patients (elderly) discontinued the treatment. Of the 4 patients from the previous study (non-elderly), 3 patients recovered or were recovering after treatment discontinuation, and 1 patient did not recover. Of the 6 new patients (elderly) who discontinued the treatment owing to akathisia, 5 patients recovered thereafter and 1 patient did not. Most of the patients who had experienced this event recovered. Of the patients who had akathisia in Study 00058, at least half experienced the event before Day 14. Akathisia often occurred in the patients in an early phase of the treatment, and the incidence of the event did not increase with an increase in the duration of the treatment. Most of the patients who had discontinued the treatment due to akathisia recovered from the event after treatment discontinuation. Given these findings, patients should be closely monitored for the occurrence of akathisia during the treatment. In the event of the occurrence of akathisia, its symptoms can be reduced if appropriate measures are taken.

Adverse drug reaction (ADR) reports submitted for extrapyramidal symptom-related events in the post-marketing setting[12)] in and outside Japan included 1088 reports on akathisia (including 44 serious ADR reports), 453 reports on tremor (including 27 serious ADR reports), 355 reports on tardive dyskinesia (including 108 serious ADR reports), 206 reports on dyskinesia (including 11 serious ADR reports), 195 reports on extrapyramidal disorder (including 27 serious ADR reports), and 108 reports on dystonia (including 36 serious ADR reports).

In light of the results from the Japanese clinical studies and other data, brexpiprazole is considered tolerable because (1) extrapyramidal symptom-related adverse events including akathisia occurred in patients receiving brexpiprazole, none of which were considered serious; and (2) most of the patients who discontinued the treatment due to the events recovered. However, because the events tended to occur more commonly in the 2 mg/day group than in the 1 mg/day group, a risk of adverse drug reactions related to the mechanism of action of brexpiprazole, such as akathisia, may increase in patients with MDD receiving brexpiprazole 2 mg. Given this risk, the applicant will include the following cautionary statement in the package insert: Patients being treated with brexpiprazole 2 mg should be periodically monitored for the relevant symptoms, and in the event of an adverse drug reaction, appropriate measures such as dose reduction or discontinuation should be taken after assessing the risks and benefits of the treatment.

PMDA's view:
Extrapyramidal symptoms including akathisia occurred more commonly in the brexpiprazole groups than in the placebo group in Study 00058. They are not events leading to a fatal outcome but are events that considerably affect the quality of life (QOL) of patients. Patients being treated with brexpiprazole should be closely monitored for the occurrence of such events. Furthermore, extrapyramidal symptoms-related adverse events including akathisia occurred more commonly in the brexpiprazole 2 mg/day group than in the 1 mg/day group in Study 00058. In view of this finding, the

12) The [redacted]th Periodic Safety Update Report (From July 10, 2015 to [redacted], 20[redacted]. Estimated number of patients exposed from [redacted] 20[redacted] to [redacted], 20[redacted] was 343987.05 person-years. Calculated from data extracted on July 22, 2022)

dosage regimen of brexpiprazole based on a balance between the safety (including the above adverse events) and the efficacy of brexpiprazole is further reviewed in Section 7.R.6.

7.R.3.3 Weight increased

Since weight increased is known to occur with antipsychotics, PMDA asked the applicant to explain about the relevant events reported by patients being treated with brexpiprazole.

The applicant's explanation:

In the Japanese phase II/III study (Study 00058), weight increased-related adverse events[13)] occurred in 2.5% (6 of 244) of patients in the placebo group, 7.2% (18 of 250) of patients in the 1 mg/day group, and 8.1% (20 of 246) of patients in the 2 mg/day group. The most commonly reported event was weight increased (6 patients in the placebo group, 18 patients in the 1 mg/day group, 19 patients in the 2 mg/day group), which tended to occur more commonly in the brexpiprazole groups than in the placebo group. Neither serious nor severe events occurred. In the Japanese long-term extension study (Study 00059), weight increased-related adverse events occurred in 33.6% (83 of 247) of patients. The most commonly reported event was weight increased (82 patients). The event leading to treatment discontinuation was weight increased, which occurred only in 7 patients. None of the events were classified as a serious or severe event. The incidences of weight increased-related adverse events in the above clinical studies were compared with those in the Japanese phase II/III study (Study 331-10-002) and Japanese long-term extension study (Study 331-10-003) of brexpiprazole in patients with schizophrenia. The comparison revealed that weight increased-related adverse events tended to be more common in patients with MDD than in patients with schizophrenia, but the types, severity, and outcome of the events did not substantially differ between the diseases.

Table 20 shows changes in body weight from baseline to the end of the double-blind period or the last assessment and the proportions of patients with ≥7% increase in body weight from baseline at the same timepoints in Study 00058. The changes tended to be higher in the brexpiprazole dose groups than in the placebo group. In Study 00059, the mean change in body weight from baseline to the last assessment was 3.27 kg, and the proportion of patients with ≥7% increase in body weight from baseline was 44.5% (110 of 247 patients). Comparison between Studies 00058 and 00059 in patients with MDD and Studies 331-10-002 and 331-10-003 in patients with schizophrenia revealed that an increase in body weight was greater in patients with MDD than in patients with schizophrenia, and the proportion patients with ≥7% increase in body weight also tended to be greater in patients with MDD than in patients with schizophrenia.

13) Events coded to the following MedDRA preferred terms (PT): Body mass index increased, obesity, overweight, weight increased, weight fluctuation, waist circumference increased, abnormal weight gain, and body mass index abnormal

Table 20. Changes in body weight in Japanese clinical studies in patients with MDD or schizophrenia (safety analysis set)

	MDD[a)]			Schizophrenia[b)]			
	Placebo	1 mg/day	2 mg/day	Placebo	1 mg/day	2 mg/day	4 mg/day
N	244	250	246	116	115	114	113
Body weigh[d)] before start of treatment[c)]	64.22 ± 14.83	64.31 ± 14.58	66.19 ± 14.66	60.8 ± 12.3	60.4 ± 13.0	61.8 ± 13.4	64.1 ± 14.2
Change[d)] from baseline at the last assessment[e)]	0.35 ± 1.45	2.01 ± 1.93	2.17 ± 2.14	-1.2 ± 2.1	-0.7 ± 2.2	0.0 ± 2.1	-0.5 ± 2.2
Proportion of patients with ≥7% increase in body weight[f)]	0.8 (2)	9.2 (23)	12.2 (30)	0.9 (1)	4.3 (5)	5.3 (6)	2.7 (3)

a) Study 00058
b) Study 331-10-002
c) For patients with MDD, the last value before the start of the double-blind period. For patients with schizophrenia, the last value before the start of the study treatment.
d) Mean ± SD (kg)
e) For patients with MDD, the value at the end of the double-blind period or the last assessment. For patients with schizophrenia, the last value at the visit scheduled in the study protocol.
f) Incidence (%) (n = number of patients with ≥7% increase in body weight)

In both Studies 00058 and 00059, weight increased-related adverse events occurred, but none of them were severe in severity. A limited number of patients experienced weight increased-related adverse events leading to treatment discontinuation. Results from clinical studies in and outside Japan showed that body weight-related adverse events occurred commonly in patients receiving brexpiprazole for a prolonged time, and many of the patients had ≥7% increase in body weight. However, body weight in some of the patients might have increased in response to brexpiprazole, which would alleviate decreased appetite, one of the MDD symptoms. Use of brexpiprazole in patients with MDD is therefore unlikely to raise clinical problems associated with weight increased.

PMDA's view:
Although the incidence of weight increased was higher in patients with MDD than in patients with schizophrenia, differences in patient characteristics relevant to weight fluctuation may have led to the different incidences. None of the patients with MDD receiving brexpiprazole experienced serious or severe weight increased. Weight increased associated with the use of brexpiprazole itself would not be a substantially problematic event in patients with depression or depressive state. However, changes in body weight should be monitored in patients treated with brexpiprazole. In the event of weight increased, its cause should be thoroughly investigated, and appropriate measures should be taken.

7.R.3.4 Convulsion- and oversedation-related adverse events

The applicant's explanation about the incidences of convulsion- and oversedation-related adverse events:
A convulsion-related adverse event[14)] reported in the Japanese phase II/III study (Study 00058) was serious epilepsy in 1 patient in the 2 mg/day group, but it occurred after the last dose of the study drug. This event was considered unrelated to the study drug. In the Japanese long-term extension study (Study 00059), no convulsion-related adverse event occurred. The analysis of integrated data from foreign studies identified serious epilepsy in 1 patient in the 1 to 3 mg/day group, but it occurred after the last dose of the study drug. This event was considered unrelated to the study drug. The analysis of integrated data from foreign extension studies identified a serious seizure in 1 patient. A Caucasian

[14)] Events coded to MedDRA SMQ "Convulsions" (narrow or broad)

male in his 30s who was receiving fluoxetine 40 mg and brexpiprazole 0.5 mg in an open-label manner in Study 331-08-212 lost consciousness for 6 seconds on Day 101 of brexpiprazole treatment and fell off a chair. After that, he restored consciousness but remained confused and could not recognize persons for 2 minutes. Then, he still had difficulty speaking for a short period of time but recovered with no other neurological symptoms. He was hospitalized owing to seizure on the same day.

ADR reports submitted in the post-marketing setting[12)] in and outside Japan included 80 reports on seizure (including 73 serious ADR reports) and 10 reports on epilepsy (including 10 serious ADR reports).

Table 21 shows oversedation-related adverse events[15)] in Studies 00058 and 00059. No serious event was reported. Adverse events leading to treatment discontinuation (malaise) occurred in 3 patients in the 2 mg/day group in Study 00058, and 2 of them had severe events. In Study 00059, malaise (in 5 patients), somnolence (in 5 patients), and fatigue (in 2 patients) occurred. For the outcome, malaise in 1 patient did not resolve, and fatigue in 1 patient resolved with sequela, but all the other events resolved. Neither analysis of integrated data from foreign clinical studies nor analysis of integrated data from foreign long-term extension clinical studies identified serious events.

Table 21. Oversedation-related adverse events (Studies 00058 and 00059, safety analysis set)

	Japanese phase II/III study (Study 00058)			Japanese long-term extension study (Study 00059)
	Placebo	1 mg/day	2 mg/day	
N	244	250	246	247
Oversedation-related adverse events	8 (3.3)	5 (2.0)	15 (6.1)	45 (18.2)
Serious adverse events	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	3 (1.2)	12 (4.9)
Adverse events reported in any group				
Somnolence	6 (2.5)	3 (1.2)	8 (3.3)	26 (10.5)
Malaise	2 (0.8)	1 (0.4)	7 (2.8)	15 (6.1)
Fatigue	0	2 (0.8)	1 (0.4)	6 (2.4)
Hypersomnia	0	0	0	1 (0.4)

n (incidence [%])

ADR reports submitted in the post-marketing setting[12)] in and outside Japan included 346 reports on somnolence (including 7 serious ADR reports), 236 reports on fatigue (including 11 serious ADR reports), and 174 reports on malaise (including 12 serious ADR reports).

In addition, the proposed package insert of brexpiprazole already includes a cautionary statement that patients should not be engaged in potentially hazardous machine operations including driving a car, in view of a potential risk associated with brexpiprazole, which may lower the convulsion threshold and cause oversedation. Based on the above, convulsion- and oversedation-related adverse events are unlikely to raise clinically relevant problems in patients with MDD.

15) Events coded to the following MedDRA PTs: Fatigue, hypersomnia, malaise, sedation, somnolence, sedation complication

PMDA's view:
Based on the submitted clinical study results, the cautionary statement about convulsion- and oversedation-related adverse events should be included in the package insert as done for the approved indication. The use of brexpiprazole in patients with depression or depressive state according to the cautionary statement is unlikely to cause convulsion- and oversedation-related adverse events that would raise clinically relevant problems.

7.R.3.5 Suicide- and hostility/aggression-related adverse events

Because (i) patients with depression are likely to be at a risk of suicide and (ii) drugs for treatment of depression including antipsychotics are reported to increase a risk of suicide, PMDA asked the applicant to explain about suicide-related adverse events[16)] in patients receiving brexpiprazole.

The applicant's explanation:
In the Japanese phase II/III study (Study 00058), suicide-related adverse events did not occur in the placebo or 2 mg/day group but occurred in 0.8% (2 of 250) of patients in the 1 mg/day group (intentional overdose in 1 patient and intentional self-injury in 1 patient). Both events occurred after the end of the treatment and then resolved. A causal relationship to the study drug was ruled out for both of them. Intentional overdose in 1 patient was classified as a serious event. In Study 00058, patients who had suicidal ideation at baseline as assessed according to the Columbia Suicide Severity Rating Scale (C-SSRS) accounted for 13.9% (34 of 244) of patients in the placebo group, 14.8% (37 of 250) of patients in the 1 mg/day group, and 15.0% (37 of 246) of patients in the 2 mg/day group, and patients who did not have suicidal ideation at baseline but newly had it during the double-blind period accounted for 6.1% (15 of 244) of patients in the placebo group, 3.2% (8 of 250) of patients in the 1 mg/day group, and 6.1% (15 of 246) of patients in the 2 mg/day group. None had suicidal behavior at baseline as assessed according to the C-SSRS, but 1 patient in the 2 mg/day group experienced it during the double-blind period. The event of suicidal behavior occurred during the follow-up period and thus was not classified as an adverse event.

In the Japanese long-term extension study (Study 00059), no suicide-related adverse events occurred. The assessments according to the C-SSRS did not identify suicidal behavior at baseline or during the treatment period. As assessed according to the C-SSRS, 10.5% (26 of 247) of patients in this study had suicidal ideation at baseline and 9.7% (24 of 247) of patients did not have suicidal ideation at baseline but newly had it later.

Trends of the incidence of suicide-related adverse events and the proportion of patients who did not have "suicidal behavior" or "suicidal ideation" at baseline but newly had it after the first dose did not differ between patients with schizophrenia and patients with MDD. The trend of the incidence of suicide-related adverse events in patients receiving brexpiprazole did not differ from those in Japanese clinical studies of other antidepressants.

ADR reports submitted in the post-marketing setting[12)] in and outside Japan included suicide-related events in 387 patients (including 355 patients with a serious event). The major events were suicidal

16) PTs coded to MedDRA SMQ "Suicide/self-injury" (narrow)

ideation in 217 patients (including 207 patients with a serious event), completed suicide in 47 patients (including 47 patients with a serious event), suicide attempt in 46 patients (including 46 patients with a serious event), and suicidal behavior in 29 patients (including 29 patients with a serious event).

As described above, Japanese clinical study results indicate that suicide-related adverse events are unlikely to occur and brexpiprazole is thus unlikely to clearly increase a risk of suicide. However, due attention should be paid to the risk of suicide in patients with depression, and the cautionary statement will therefore be included in the package insert as done for other antidepressants.

Because there are concerns about increased hostility/aggression associated with the use of atypical antipsychotics, PMDA asked the applicant to explain about hostility/aggression-related adverse events[17] in patients receiving brexpiprazole.

The applicant's explanation:
Table 22 shows the incidences of hostility/aggression-related adverse events in Studies 00058 and 00059. There were no serious events. Two patients discontinued the treatment owing to mania in Study 00058 but both recovered from the event.

Table 22. Hostility/aggression-related adverse events (Studies 00058 and 00059, safety analysis set)

	Japanese phase II/III study (Study 00058)			Japanese long-term extension study (Study 00059)
	Placebo	1 mg/day	2 mg/day	
N	244	250	246	247
Hostility/aggression-related adverse events	1 (0.4)	4 (1.6)	2 (0.8)	1 (0.4)
Serious adverse events	0	0	0	0
Adverse events leading to treatment discontinuation	0	1 (0.4)	1 (0.4)	0
Adverse events reported in any group				
Hypomania	0	1 (0.4)	0	0
Irritability	0	2 (0.8)	1 (0.4)	0
Mania	1 (0.4)	1 (0.4)	1 (0.4)	0
Affect lability	0	0	0	1 (0.4)

n (incidence [%])

ADR reports in the post-marketing setting[18] outside Japan included hostility/aggression-related adverse events in 472 patients with MDD (including 52 patients with a serious event). The major adverse events were agitation in 211 patients (including 3 patients with a serious event), mania in 165 patients (including 11 patients with a serious event), and irritability in 52 patients (including 4 patients with a serious event).

As described above, clinical study data do not suggest that brexpiprazole tends to clearly increase a risk of hostility/aggression. Since due attention should be paid to the risk of hostility/aggression as with the risk of suicide in patients with depression, the cautionary statement will be included in the package insert as done for other antidepressants.

17) PTs coded to MedDRA SMQ "Hostility/aggression" (broad)
18) Foreign post-marketing safety information up to July 9, 2022 (estimated number of patients exposed = 892.0 per 1000 person-years). Including a total of 5398 patients with MDD who experienced adverse events.

PMDA's view:
In view of the submitted clinical study data, use of brexpiprazole in patients with depression or depressive state is unlikely to clearly increase a risk of suicide or hostility/aggression-related adverse events. It is appropriate for the applicant to include the cautionary statement in the package insert as done for other antidepressants.

7.R.3.6 Impact of type of a concomitant antidepressant on the safety of brexpiprazole

PMDA asked the applicant to explain the impact of type of a concomitant antidepressant (SSRI, SNRI, or mirtazapine) on the safety of brexpiprazole.

The applicant's explanation:
Table 23 shows the incidences of adverse events by type of concomitant antidepressants used in Japanese clinical studies (Studies 00058 and 00059). Although the sample sizes were limited, the incidences of all the adverse events and serious adverse events did not greatly differ regardless of the type of concomitant antidepressants, including a potent CYP2D6 inhibitor (paroxetine). Although the sample sizes were limited, adverse events leading to treatment discontinuation tended to more commonly occur in patients receiving mirtazapine, but adverse events except hypertension (in 1 patient) were noted in patients receiving other antidepressants (SSRI and SNRI) as well. None of them were severe or serious.

Based on the above, the safety of brexpiprazole is unlikely to differ regardless of the types of concomitant antidepressants.

Table 23. Incidences of adverse events by type of a concomitant antidepressant

	Japanese phase II/III study (Study 00058)						Japanese long-term extension study (Study 00059)	
	Placebo		1 mg/day		2 mg/day		2 mg/day	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Any adverse event	244	144 (59.0)	250	155 (62.0)	246	182 (74.0)	247	231 (93.5)
Duloxetine	39	22 (56.4)	46	31 (67.4)	47	36 (76.6)	38	33 (86.8)
Escitalopram	69	35 (50.7)	81	48 (59.3)	77	59 (76.6)	67	62 (92.5)
Fluvoxamine	10	7 (70.0)	9	5 (55.6)	10	9 (90.0)	9	9 (100.0)
Milnacipran	8	8 (100.0)	5	2 (40.0)	5	3 (60.0)	8	8 (100.0)
Mirtazapine	-	-	-	-	-	-	7	7 (100.0)
Paroxetine	16	9 (56.3)	11	9 (81.8)	12	10 (83.3)	17	16 (94.1)
Sertraline	72	45 (62.5)	77	48 (62.3)	77	51 (66.2)	78	74 (94.9)
Venlafaxine	30	18 (60.0)	21	12 (57.1)	18	14 (77.8)	23	22 (95.7)
Serious adverse events	244	2 (0.8)	250	3 (1.2)	246	3 (1.2)	247	9 (3.6)
Duloxetine	39	0	46	1 (2.2)	47	0	38	1 (2.6)
Escitalopram	69	1 (1.4)	81	2 (2.5)	77	1 (1.3)	67	3 (4.5)
Fluvoxamine	10	0	9	0	10	0	9	0
Milnacipran	8	0	5	0	5	0	8	0
Mirtazapine	-	-	-	-	-	-	7	0
Paroxetine	16	0	11	0	12	0	17	0
Sertraline	72	1 (1.4)	77	0	77	2 (2.6)	78	4 (5.1)
Venlafaxine	30	0	21	0	18	0	23	1 (4.3)
Adverse events leading to treatment discontinuation	244	3 (1.2)	250	2 (0.8)	246	18 (7.3)	247	66 (26.7)
Duloxetine	39	0	46	0	47	2 (4.3)	38	11 (28.9)
Escitalopram	69	1 (1.4)	81	0	77	11 (14.3)	67	18 (26.9)
Fluvoxamine	10	0	9	1 (11.1)	10	1 (10.0)	9	5 (55.6)
Milnacipran	8	0	5	0	5	1 (20.0)	8	2 (25.0)
Mirtazapine	-	-	-	-	-	-	7	6 (85.7)
Paroxetine	16	0	11	0	12	0	17	3 (17.6)
Sertraline	72	2 (2.8)	77	1 (1.3)	77	2 (2.6)	78	17 (21.8)
Venlafaxine	30	0	21	0	18	1 (5.6)	23	4 (17.4)

-: Not applicable

Results from foreign clinical studies in patients with MDD (Studies 331-10-227, 331-10-228, 331-13-214, 331-10-238, 331-12-282, 14570A, 331-08-211, 331-09-222, 16160A, and 331-08-212) also showed that the incidences of serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose reduction did not greatly differ regardless of the type of concomitant antidepressants. The analysis of pooled data from foreign clinical studies[10)] showed that the incidence of adverse events in patients receiving brexpiprazole concomitantly with paroxetine was 50.0% (64 of 128 patients) in the pooled placebo group and 57.9% (95 of 164 patients) in the pooled brexpiprazole 1 to 3 mg group, with no substantial difference between the placebo and brexpiprazole groups. The events that occurred in ≥5% of patients in the pooled brexpiprazole 1 to 3 mg group and more commonly in the pooled brexpiprazole 1 to 3 mg group than in the pooled placebo group were weight increased (1.6% in the pooled placebo group and 7.3% in the pooled brexpiprazole 1 to 3 mg group) and akathisia (5.5% and 10.4%). The safety profile of brexpiprazole did not differ greatly from those of other antidepressants.

Based on the above findings, the safety of brexpiprazole by concomitant antidepressant did not tend to differ regardless of the type of concomitant antidepressants, including a potent CYP2D6 inhibitor (paroxetine).

PMDA's view:
Based on the submitted clinical study data, the safety of brexpiprazole did not tend to differ regardless of the types of concomitant antidepressants, including paroxetine, known as a potent CYP2D6 inhibitor, although the interpretation of the data is limited because the numbers of patients receiving a particular antidepressant concomitantly with brexpiprazole are small.

7.R.4 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of brexpiprazole.

The applicant's explanation:
According to the guideline for treatment of depression supervised by the Japanese Society of Mood Disorders (Guideline for Treatment of Depression, version 2, Igaku-Shoin; 2017), the mainstay for treatment of moderate to severe MDD is drug therapy with antidepressants. Although SSRI, SNRI, and mirtazapine are listed as the first-line drugs, the remission rate in patients treated with these antidepressants is approximately 30% to 40% (*Psychiatria et Neurologia Japonica.* 2003;105:1318). For patients who have not successfully responded to the first-line drug, the following strategy is recommended: Increase the dose of the current antidepressant to an adequate level at which the adverse effect would not cause clinical problems, and continue treatment at the increased dose for approximately 4 weeks; and for patients who still have hardly responded to the first-line drug at the increased dose, change the drug; or for patients who have shown improvements in some of depressive symptoms but are not expected to achieve further improvements, use a drug for augmentation of antidepressants.

Drugs used for augmentation of antidepressants include lithium, triiodothyronine/levothyroxine (T3/T4), lamotrigine, valproic acid, carbamazepine, and atypical antipsychotics. The efficacy of augmentation of antidepressants with the above drugs except atypical antipsychotics has not been sufficiently demonstrated because of the limited data on their concomitant use with SSRI or SNRI or for other reasons. An atypical antipsychotic drug approved in Japan for use as an augmentation therapy is aripiprazole.

In the Japanese phase II/III study (Study 00058) conducted as a confirmatory study, brexpiprazole was used for augmentation of an antidepressant (SSRI or SNRI) in patients with MDD who had inadequately responded to appropriate antidepressant treatment, and its superiority to placebo was demonstrated [see Section 7.R.2]. Results from Study 00058 and the Japanese long-term extension study (Study 00059) suggest that brexpiprazole has acceptable safety [see Section 7.R.3].

In addition to the above clinical study data, the guideline for treatment of depression used in Japan recommends that use of a drug for augmentation of existing antidepressant therapy should be considered as an option for the treatment of patients who have inadequately responded to antidepressants. Based on the above considerations, brexpiprazole can be positioned as one of drugs used for augmentation of existing antidepressant therapy in patients with depression or depressive state who have inadequately responded to antidepressants such as SSRI or SNRI.

PMDA's view:
The submitted clinical study data have demonstrated that brexpiprazole has efficacy in the augmentation of existing antidepressant therapy and acceptable safety [see Sections 7.R.2 and 7.R.3]. The guideline for treatment of depression used in Japan recommends augmentation therapy as one of the measures taken in patients who have inadequately responded to antidepressants and then the use of concomitant atypical antipsychotics as one approach for augmentation of existing antidepressant therapy. However, the guideline also states that the use of concomitant atypical antipsychotics should not be initiated without careful consideration on their adverse effects such as akathisia, and that atypical antipsychotics should not precede other drugs for antidepressant augmentation therapy. In view of the above, as with aripiprazole, brexpiprazole is positioned as one of the treatment options in patients with depression or depressive state who have inadequately responded to treatment with existing antidepressants such as SSRI or SNRI and who opt for the use of an atypical antipsychotic for augmentation of existing antidepressant therapy.

Of note, the guideline for treatment of depression used in Japan further states that whether the long-term use of atypical antipsychotics for augmentation of antidepressants is clinically appropriate remains unclear because of the limited clinical study data. The applicant is therefore required to appropriately disseminate the following precaution through materials for healthcare professionals: The duration of treatment with brexpiprazole should be carefully considered based on clinical study data on brexpiprazole obtained in and outside Japan in view of the limited results from placebo-controlled long-term extension studies of atypical antipsychotics including brexpiprazole used for augmentation of antidepressants.

7.R.5 Indication

In view of review in Sections 7.R.1 to 7.R.4, PMDA has concluded that the "Indication" of brexpiprazole should be "Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy)" as with that of aripiprazole, which is approved for augmentation of antidepressants, and the "Precautions Concerning Indications" section should include the cautionary statement that "Brexpiprazole should be used concomitantly with an antidepressant only in patients who had an inadequate response to appropriate treatment with antidepressants such as SSRI and SNRI."

7.R.6 Dosage and administration

The applicant's explanation about the "Dosage and Administration" of brexpiprazole:
In a foreign clinical study where brexpiprazole was started at 0.5 or 1 mg/day, the safety of brexpiprazole did not differ between these starting doses. For this reason, in the Japanese phase II/III study (Study 00058), brexpiprazole was started at 1 mg/day in both brexpiprazole groups to reach the effective dose earlier. The incidence of adverse events up to Day 7 was 22.0% (55 of 250 patients) in the 1 mg/day group and 27.2% (67 of 246 patients) in the 2 mg/day group, both of which did not greatly differ from 23.0% (56 of 244 patients) in the placebo group. Adverse events reported in the 1 mg/day and 2 mg/day groups up to Day 7 included only a serious event in 1 patient in the 1 mg/day group and events leading to treatment discontinuation in 2 patients in the 2 mg/day group. Thus, the

starting dose of 1 mg/day was well tolerated. Based on the above findings, 1 mg/day was selected as the starting dose of brexpiprazole.

In Study 00058, statistically significant differences were observed between the 1 mg/day or 2 mg/day group and the placebo group, and both brexpiprazole doses caused no considerable safety problems and were well tolerated. However, the incidence of akathisia and other events increased with an increase in the dose. In view of these results, the applicant considered that the following dosage regimen should be proposed: The usual dose is 1 mg/day of brexpiprazole, and the dose may be adjusted according to the patient's condition but should not exceed 2 mg/day.

In Study 00058, differences between the 1 mg/day and placebo groups and between the 2 mg/day and placebo groups were similar for both the primary and secondary endpoints, while the incidence of adverse drug reactions such as akathisia tended to increase with an increase in the dose of brexpiprazole. In view of these findings, PMDA asked the applicant to explain whether stating that "the dose may be adjusted according to the patient's condition but should not exceed 2 mg/day" is appropriate as the dosage and administration of brexpiprazole for the treatment of depression or depressive state.

The applicant's explanation:
In Study 00058, a change in MADRS total score from baseline to the end of the double-blind period (least mean square ± SE), the primary endpoint, was −6.7 ± 0.47 in the placebo group, −8.5 ± 0.47 in the 1 mg/day group, and −8.2 ± 0.47 in the 2 mg/day group. Statistically significant differences from placebo were observed in both brexpiprazole groups. The change from baseline was greater in the 1 mg/day group than in the 2 mg/day group in terms of the numerical value, but a difference between the 1 mg/day and 2 mg/day groups (the point estimate and SE) is 0.3 and 0.66, which fall within a range of variations. The applicant therefore considers it unreasonable to conclude that the efficacy of brexpiprazole at 2 mg/day is inferior to that at 1 mg/day. In addition, although the results on the primary endpoint did not greatly differ between the 1 mg/day and 2 mg/day groups in Study 00058, data only from a single study are considered insufficient to support a dose-response relationship in patients with MDD, who are highly heterogeneous.

The foreign phase III study (b) (Study 228) and foreign phase III study (c) (Study 214) included only the 2 mg/day group, in which results were found to differ from those in the placebo group with a statistical significance. On the other hand, in the foreign phase III study (a) (Study 227), which included the 1 mg/day and 3 mg/day groups, no statistically significant difference was observed between the 1 mg/day group and placebo group. Studies 00058 and 227 had similar designs and characteristics of patients enrolled without considerable differences, and a reason for the failure to demonstrate the efficacy of brexpiprazole 1 mg/day in Study 227 remains unknown. However, Study 227 suggested that the dose of 1 mg/day tended to have efficacy. The results of Study 227 did not necessarily deny the efficacy of brexpiprazole 1 mg/day. A meta-analysis for a dose-response relationship using data from 6 foreign clinical studies conducted to optimize the dose of brexpiprazole yielded a dose-response curve of brexpiprazole, in which the response increased over a dose range from 1 to 2 mg (*Psychiatry Clin Neurosci.* 2022;76:416-22). Another meta-analysis for a

dose-response relationship using data from a total of 7 studies, including the above 6 studies plus Study 00058, performed in a similar manner yielded similar results. Based on the above findings, results from the 1 mg/day group in Studies 00058 and 227 and data from the meta-analyses for a dose-response relationship indicate that 1 mg/day is an effective dose close to the minimum effective dose, while 2 mg/day is a robustly effective dose that has consistently yielded statistically significant improvements in multiple clinical studies. There should be no problem in the analysis using results pooled from Japanese and foreign studies because comparisons of steady-state plasma brexpiprazole concentrations at <6 hours post-dose (around the peak) and 20 to 28 hours post-dose (around the trough) between Study 00058 and foreign studies (Studies 227 and 228) revealed no considerable differences between Japanese and non-Japanese patients (see Table 24), indicating no ethnic differences in the pharmacokinetics of brexpiprazole.

Table 24. Plasma brexpiprazole concentrations (ng/mL) in patients with MDD after administration of brexpiprazole 1 or 2 mg

	1 mg/day		2 mg/day	
Sampling point[a)]	0-6 hours post-dose	20-28 hours post-dose	0-6 hours post-dose	20-28 hours post-dose
Japanese study (Study 00058)	36.7 [24.4, 70.9]	29.5 [13.0, 49.4]	70.7 [33.6, 123.2]	55.1 [21.0, 116.1]
Foreign studies (Studies 227 and 228)	33.7 [15.2, 59.2]	26.4 [9.0, 46.9]	74.5 [29.3, 127.0]	42.5 [14.3, 86.4]

Median [10th percentile, 90th percentile]
a) Time after the last dose

To discuss whether a dose increase to 2 mg of brexpiprazole in patients who had an inadequate response to 1 mg is meaningful, the applicant analyzed data from patients who entered Study 00059 after the completion of Study 00058 and had an inadequate response at the end of the double-blind period in Study 00058 (<50% reduction in MADRS total score from baseline). In patients who entered Study 00059 after receiving 1 mg/day in Study 00058, the MADRS responder rate increased over a period from 2 weeks after entry into Study 00059 (Week 2) to Week 8, reaching 26.32% (15 of 57 patients) at Week 8, while in those who entered Study 00059 after receiving 2 mg/day in Study 00058, the MADRS responder rate remained almost unchanged, reaching 11.43% (4 of 35 patients) at Week 8. The above finding suggested that some of the patients who had had an inadequate response to 1 mg/day might have achieve an adequate response to the increased dose (2 mg/day).

In view of opinions from experts and the status of use of antipsychotics for the treatment of depression in clinical settings in and outside Japan described below, the dosage range should be widen by providing not only the recommended dose (1 mg/day) but also an option to increase the dose to 2 mg/day.

- In foreign Studies 227 and 228, the primary endpoint was the mean change in MADRS total score from baseline (the end of the antidepressant treatment period) to 6 weeks after start of treatment with the study drug (Week 6), and differences [95% CI] in the results on the primary endpoint between the 2 mg/day and placebo groups in Study 228 and between the 3 mg/day and placebo groups in Study 227 were −3.21 [−4.87,−1.54][19)] and −1.95 [−3.39,−0.51][20)], respectively. Although a dose-response relationship at doses ≥2 mg is unclear, the US labeling states the following doses

[19)] Analysis performed by MMRM (with an unstructured correlation structure). The model included treatment group, study center, timepoint, interaction between the treatment group and timepoint, and interaction between baseline MADRS total score (at Week 8 of the antidepressant treatment period) and timepoint. The analysis used the predetermined efficacy analysis set comprised of subjects meeting the revised criteria included in the Protocol Amendment 3.

for an adjunctive therapy of MDD, approved based on results from these foreign phase III studies (Studies 227 and 228): The starting dose of 0.5 to 1 mg/day, the recommended dose of 2 mg/day, and the maximum tolerable dose of 3 mg/day. An investigation of distribution of brexpiprazole prescriptions for patients with MDD by dose in the US (a total of 702,840 prescriptions issued in 2022) revealed that the prescriptions for the doses of <2 mg/day, 2 mg/day, and >2 mg/day accounted for 51%, 29%, and 20%, respectively, indicating that the dose of >2 mg/day, which exceeds the recommended dose (2 mg/day) in the US, is prescribed to a certain number of patients. In the US, brexpiprazole is approved for the treatment of schizophrenia in adults at the starting dose of 1 mg/day, the recommended dose of 2 to 4 mg/day, and the maximum dose of 4 mg/day.

- The dosage regimen of aripiprazole approved for the treatment of depression or depressive state in Japan specifies that the usual dose is 3 mg/day, and that the dose may be adjusted according to the patient's age and symptoms, but should not exceed 15 mg/day. According to the specified use-results survey (1103 patients; mean duration of treatment, 253.7 ± 169.8 days), patients with depression or depressive state who received aripiprazole at the mean daily doses of <3 mg, 3 mg, and >3 mg accounted for 14.5% (160 of 1103 patients), 63.7% (703 of 1103 patients), and 21.8% (240 of 1103 patients), respectively, of the overall survey population, indicating that the dose of >3 mg/day is prescribed to a certain number of patients.

To define the patient population who needs to have the brexpiprazole dose increased to 2 mg, the applicant examined opinions from experts who reviewed the status of prescription of aripiprazole in clinical practice and reached the view that the increased dose (2 mg/day) would be a treatment option in patients who are considered to have an inadequate response to the recommended dose, such as failing to meet the individual treatment goal. In addition, the applicant considered that the assessment of the patient's clinical response to brexpiprazole for determining whether to increase the dose to 2 mg/day should occur at 6 weeks after the start of the treatment because in Study 00058, an improving trend was observed in both 1 mg/day and 2 mg/day groups, beginning at 2 weeks after the start of administration of placebo or brexpiprazole, and the trend continued for 6 weeks [see Section 7.R.1.2].

The safety of brexpiprazole at 2 mg/day was assessed. In Study 00058, adverse events leading to discontinuation of the study drug commonly occurred in the brexpiprazole 2 mg/day group, but all of them resolved or were resolving after treatment discontinuation, except for malaise (in 2 patients) which remained unresolved. Of the 2 unrecovered patients, one discontinued the treatment owing to sedation at 1 mg/day before the dose increase. The incidence of serious adverse events did not differ between the dose groups. There were no considerable problems with the safety of brexpiprazole 2 mg. Even compared with the safety of aripiprazole approved for the treatment of depression or depressive state, the safety of brexpiprazole 2 mg is considered acceptable.

As described above, the safety of brexpiprazole 2 mg/day is acceptable, but from a viewpoint of ensuring the proper use of the drug, the dose should be increased to 2 mg/day only in patients who are considered to have an inadequate response, such as failing to meet the individually set treatment goal, because (1) the incidence of adverse events was higher in the 2 mg/day group than in the 1 mg/day group in the Japanese clinical study; and (2) adverse events leading to treatment discontinuation, such

as akathisia and malaise, most of which are induced by the mechanism of action of brexpiprazole, commonly occurred. Whether to increase the dose to 2 mg/day should be assessed at Week 6, and then the continued need for the treatment should be determined at an interval of approximately 6 weeks. Furthermore, to prevent the dose of brexpiprazole from being increased without careful consideration, cautionary statements should be included in the package insert, materials, etc. Based on the above, the applicant will modify the proposed dosage and administration as follows:

Modified Dosage and Administration (draft)
The usual adult dosage is 1 mg of brexpiprazole orally administered once daily. The dose may be increased to 2 mg/day only in patients who are tolerant of the current dose but have an inadequate response to it.

In addition, the "Precautions Concerning Dosage and Administration" section will include the following cautionary statements.

- Brexpiprazole should be used concomitantly with antidepressants such as SSRI and SNRI. The efficacy of brexpiprazole alone in patients with depression or depressive state is not confirmed.
- The dose of brexpiprazole should be maintained at the minimum necessary level. An increase of the dose of brexpiprazole to 2 mg should be considered around 6 weeks after the start of the treatment.
- After the dose increase, the continued need for treatment with brexpiprazole 2 mg should be determined at an interval of approximately 6 weeks. If the expected response is not achieved, the treatment should not be continued unnecessarily.

PMDA's view:
Based on the results of Study 00058 and other data, the starting dose of 1 mg/day is appropriate.

In Study 00058, the point estimate of a difference in results on the primary endpoint between the 2 mg/day and placebo groups was similar to that between the 1 mg/day and placebo groups, and a similar trend was observed for all the secondary endpoints. Study 00058 did not yield the data suggesting that the efficacy of brexpiprazole at 2 mg/day would be greater than that at 1 mg/day. From a viewpoint of the efficacy, the recommended dose of 1 mg/day in Japan is appropriate. The applicant explained that the tolerability of brexpiprazole even at 2 mg/day was confirmed, but in Study 00058, the safety profile of brexpiprazole at 1 mg/day is more favorable than that at 2 mg/day because the incidences of mild to moderate events and events leading to treatment discontinuation were higher at 2 mg/day than at 1 mg/day, although deaths and severe events do not tend to occur more commonly at 2 mg/day.

Based on the above, the recommended dose of brexpiprazole in Japan should be 1 mg/day, at which the benefit-and-risk balance of brexpiprazole is optimal.

PMDA's view on the appropriateness of additionally including 2 mg/day in the dosage regimen:
In view of the following points in addition to the results of Study 00058, the submitted study data do not present a clear answer as to whether the increased dose (2 mg/day) would enhance the effect of brexpiprazole in patients with an inadequate response to 1 mg/day.

- Because the pharmacokinetics of brexpiprazole did not greatly differ between Japanese and non-Japanese patients, based on the results of the meta-analysis of pooled data from 6 foreign clinical studies and Study 00058 for a dose-response relationship, the applicant discussed a dose-response relationship in Japanese patients with MDD over a range from 1 mg/day to 2 mg/day. However, a possibility of brexpiprazole presenting different dose-response relationships in Japanese and non-Japanese patients cannot be ruled out because of the following points: (i) Study 227, only a foreign clinical study investigating 1 mg/day, did not demonstrated the efficacy of brexpiprazole at 1 mg/day; and (ii) the approved dose for the approved indication of brexpiprazole differs between Japanese and non-Japanese patients. In addition, the dose-response curves yielded using data from 6 foreign clinical studies (including 1 study with data at 1 mg/day) and from the same 6 foreign studies and 1 Japanese clinical study did not greatly differ, but this finding does not necessarily suggest that the effect would increase with the increasing dose from 1 mg/day to 2 mg/day in Japanese patients with MDD.
- The applicant, however, claimed that the results of Study 00059 in patients who had an inadequate response at the end of Study 00058 before entering Study 00059 suggested that the increased dose (2 mg/day) enhances the effect in patients with an inadequate response to 1 mg/day. The comparison, however, was made between populations of inadequate responders in the 1 mg/day group and of those in the 2 mg/day group, which had different patient characteristics, not forming proper evaluation of the effect of the increased dose in inadequate responders to 1 mg/day. Furthermore, Study 00059 was conducted in an open-label uncontrolled manner, leaving the effects of the natural course of the disease and the placebo being confounded. The MADRS responder rate in Study 00059, presented by MADRS non-responders from Study 00058 does not suggest a possibility that there are some patients who had an inadequate response to 1 mg/day but gained a first response to the increased dose (2 mg/day).

The efficacy results by patient characteristic in Study 00058 did not identify the potential population in which increased efficacy could be expected at a higher dose (2 mg/day), from viewpoints of medicine and mechanism of action of brexpiprazole. Thus, such analysis cannot serve to define the patient population that requires the dose exceeding the recommended dose.

In addition, brexpiprazole should be administered at the minimum dose level if a similar response is achieved at different dose levels, on the basis of the following considerations: (1) The submitted study data show that the safety profile of brexpiprazole at 1 mg/day is more favorable than that at 2 mg/day in Japanese patients, and specifically, the incidence of extrapyramidal symptoms-related adverse events such as akathisia increased dose-dependently in Study 00058; and (2) the guideline for treatment of depression states that the use of concomitant atypical antipsychotics should not be initiated without careful consideration on their adverse effects such as akathisia, and that atypical antipsychotics should not precede other drugs for antidepressant augmentation therapy.

However, PMDA will make final decisions on whether the increased dose (2 mg/day) should be included in the dosage regimen and whether there is a clinical need for the increased dose, taking account of the pathology of depression and the clinical positioning of brexpiprazole as well as comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing investigations in patients with MDD:

Information on the safety of brexpiprazole in patients with depression or depressive state should be collected through routine pharmacovigilance activities, with no additional pharmacovigilance activities, for the following reasons: (1) Results from the Japanese clinical studies (Studies 00058 and 00059) have identified no additional events of interest for use in patients with depression or depressive state, in comparison with the approved use in those with schizophrenia; (2) currently available post-marketing information on adverse drug reactions in patients with schizophrenia in Japan has not raised additional safety concerns; and (3) foreign post-marketing experience with brexpiprazole for use in patients with depression or depressive state has not raised additional safety concerns either [see Section 7.R.3].

PMDA's view:

The applicant plans to collect post-marketing safety information through routine pharmacovigilance activities, with no additional pharmacovigilance activities, and will consider additional pharmacovigilance activities, where necessary. In view of the review in Section 7.R.3, the above applicant's plan is acceptable because the events reported by patients with depression or depressive state receiving brexpiprazole are events known to occur with use of brexpiprazole for the approved indication or use of antidepressants.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-01) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that brexpiprazole has efficacy as an augmentation therapy in patients with depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy), and that brexpiprazole has acceptable safety in view of its benefits. Brexpiprazole has clinical significance because it offers a new treatment option for augmentation of antidepressants.

PMDA has concluded that brexpiprazole may be approved if brexpiprazole is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 27, 2023

Product Submitted for Approval

Brand Name	(a) Rexulti Tablets 1 mg (b) Rexulti Tablets 2 mg (c) Rexulti OD Tablets 0.5 mg (d) Rexulti OD Tablets 1 mg (e) Rexulti OD Tablets 2 mg
Non-proprietary Name	Brexpiprazole
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	January 30, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the design of the Japanese phase II/III study described in the Review Report (1).

1.1 Efficacy

The expert advisors commented below and supported PMDA's conclusion described in Section "7.R.2 Efficacy" of the Review Report (1).

- The following PMDA's conclusion is appropriate: In the Japanese phase II/III study (Study 00058), study treatment was discontinued in 11.0% (27 of 246) of patients in the 2 mg/day group during the double-blind period, and study treatment was discontinued in a total of 16 patients in all the groups owing to deviation from the protocol [see Section 7.1 of the Review Report (1)]. To assess an impact of the missing data, a sensitivity analysis (placebo multiple imputation and tipping point analysis) was performed on the assumption that data were missing not at random (MNAR). Based on the analysis result, the missing data associated with discontinuation had a limited potential impact on the evaluation of the efficacy of brexpiprazole.

1.2 Safety

The expert advisors supported PMDA's conclusions described in Section "7.R.3 Safety" of the Review Report (1), including conclusion that extrapyramidal symptoms including akathisia in patients receiving brexpiprazole are not events leading to fatal outcome but substantially affect the QOL of patients, and thus patients being treated with brexpiprazole should be closely monitored for the occurrence of such events.

In addition, the expert advisors pointed out that extrapyramidal symptoms induced by antipsychotics such as brexpiprazole include not only reversible symptoms such as akathisia that may resolve after treatment discontinuation or dose reduction but also irreversible symptoms such as tardive dyskinesia, and that the risk of extrapyramidal symptoms including tardive dyskinesia should be carefully discussed. Then, the following comments on akathisia and tardive dyskinesia were raised from the expert advisors.

Akathisia

- In the Japanese phase II/III study in patients with MDD (Study 00058), the incidence of akathisia was 6.0% (15 of 250 patients) in the 1 mg/day group and 24.4% (60 of 246 patients) in the 2 mg/day group, showing higher incidence than 1.7% (2 of 115 patients) in the 1 mg/day group and 3.5% (4 of 114 patients) in the 2 mg/day group in the Japanese clinical study involving patients with schizophrenia (Study 331-10-002) (see Table 18). In addition, the incidence of akathisia in the 2 mg/day group in the Japanese clinical study was higher than those in foreign clinical studies in patients with MDD as follows: 4.4% (10 of 226 patients) in the 1 mg/day group and 13.5% (31 of 229 patients) in the 3 mg/day group in Study 227; 7.4% (14 of 188 patients) in the 2 mg/day group in Study 228; and 8.3% (16 of 192 patients) in the 2 mg/day group in Study 214. The cause of a trend toward the higher incidence of akathisia in Japanese patients with MDD treated with 2 mg/day should be discussed. Furthermore, if patient characteristics that may associated with the occurrence of akathisia are identified, the caution about such information should be raised.
- In Study 00058, only 4.9% (12 of 246) of patients in the 2 mg/day group experienced extrapyramidal symptoms-related adverse events leading to discontinuation (see Table 19), but as large as 19.9% (49 of 246) of patients used anticholinergic antiparkinson drugs, of which concomitant use was allowed for the treatment of extrapyramidal symptoms. Whether the use of brexpiprazole should be continued with additional concomitant drugs for the treatment of extrapyramidal symptoms must be carefully decided for individual patients in view of adverse reactions to brexpiprazole and other treatment options.
- In the Japanese long-term extension study (Study 00059), the incidence of akathisia in newly enrolled patients (elderly) was higher than that in patients from Study 00058 (non-elderly), and the incidence of adverse events leading to treatment discontinuation was also higher (Table 14) in the former patients. The applicant should appropriately provide the above information to healthcare professionals.

Tardive dyskinesia

- When brexpiprazole is used in patients with depression, the risk of tardive dyskinesia associated with its long-term use should be avoided, wherever possible, in view of the following points: (1)

Long-term use of high-dose antipsychotics is reported to increase the risk of tardive dyskinesia, especially in the elderly; (2) MDD often spontaneously remits in approximately 3 months without aggressive treatment with potent drugs; and (3) in routine clinical practice in Japan, medication is often interrupted once the patient has shown improvement, and it will be resumed if the disease has recurred or relapsed.

- Because tardive dyskinesia induced by the long-term use of antipsychotics is highly difficult to treat, the occurrence of tardive dyskinesia must be prevented. In routine clinical practice, however, no established useful means to predict the occurrence of tardive dyskinesia are available at present, and thus healthcare professionals must be aware that there is no other effective measure but to ensure that brexpiprazole is used only when necessary.

In view of comments raised from the expert advisors in the Expert Discussion, PMDA requested the applicant to discuss patient characteristics that may be associated with the occurrence of akathisia and tardive dyskinesia in Japanese patients with MDD and to raise caution and provide information, as necessary, based on the clinical study data and the above discussion.

The applicant's explanation about akathisia and tardive dyskinesia:

Akathisia

In clinical studies of brexpiprazole, the incidence of akathisia tended to be higher in patients with MDD than in patients with schizophrenia. This finding is considered to reflect the predisposition of patients with MDD who may be susceptible to akathisia because akathisia is mainly associated with the blockade of dopamine receptors (*Biol Psychiatry.* 2009;66:201-5); and this is based on a theory that the brain's reward system function is overactivated in patients with schizophrenia, while the brain's reward system dysfunction underlies depressive symptoms.

The incidence of akathisia tended to be higher in the Japanese clinical studies of brexpiprazole than in the foreign clinical studies. Whether the race had an impact on the incidence of akathisia in patients receiving brexpiprazole is unclear because the incidence of akathisia in the 1 mg/day group in the Japanese clinical study (Study 00058) was similar to that in the foreign clinical study (Study 227), although a meta-analysis using data from 56 clinical studies in patients with schizophrenia, bipolar disorder, or MDD suggested that the incidence of akathisia was low in clinical studies including a large number of Caucasian patients. The meta-analysis was performed to compare the incidences of akathisia induced by antipsychotics including brexpiprazole (*CNS Drugs.* 2019:33;549-66).

In addition, an investigation did not identify patient characteristics, including the starting dose and timing of the dose increase, that might have an impact on the occurrence of akathisia in patients with MDD.

At present, no attributes other than the dose have been identified as factors that may have an impact on the occurrence of akathisia in Japanese patients with MDD.

Tardive dyskinesia

Because tardive dyskinesia did not occur in Japanese and foreign clinical studies, discussion about patient characteristics that might have an impact on the occurrence of tardive dyskinesia was not feasible. According to the Japanese and foreign post-marketing safety information,[20)] 350 events of tardive dyskinesia in 349 patients (0.39 per 1000 person-years) were reported outside Japan, including 182 events in 181 patients with depression (0.20 per 1000 person-years), 20 events in 20 patients with schizophrenia (0.02 per 1000 person-years), and 149 events in 149 patients with unknown disease (0.17 per 1000 person-years). Serious events included 61 events in 60 patients with depression (0.07 per 1000 person-years), 5 events in 5 patients with schizophrenia (0.01 per 1000 person-years), and 37 events in 37 patients with unknown disease (0.04 per 1000 person-years). In Japan, 12 events of tardive dyskinesia in 12 patients (0.03 per 1000 person-years, all with schizophrenia) were reported, including 5 serious events in 5 patients (0.01 per 1000 person-years). The number of reports were small both in and outside Japan without any considerable difference. Although discussion based on spontaneous reports, etc. has limitations, a subgroup analysis by disease did not identify any specific risk in terms of patient characteristics. In addition, the number of reported events per 1000 person-years was as small as <0.5 in all subgroups of disease, and the incidence rate of serious events did not greatly differ among subgroups of disease. Based on the above findings, the applicant considers that patients with depression are unlikely to present a special risk of tardive dyskinesia.

Of note, the Manuals for Management of Individual Serious Adverse Drug Reactions – Dyskinesia (Ministry of Health, Labour and Welfare, May 2009 [revised in February 2022]) state that tardive dyskinesia is a symptom associated with the long-term use of antipsychotics. While a report on risk factors of tardive dyskinesia was published (*Japanese Journal of Clinical Psychopharmacology.* 2023;26:367-73), there is a report denying the above concept (*Neurol Clin.* 2011;29:127-48). After all, a literature survey on tardive dyskinesia did not identify a risk factor either.

As described above, at present, no attributes other than the duration of the treatment have been identified as factors that may have an impact on the occurrence of tardive dyskinesia in Japanese patients with MDD. Since the package insert has already included a cautionary statement that tardive dyskinesia may occur in association with the long-term use of brexpiprazole, no additional cautionary statement is considered necessary.

PMDA's view:

The applicant's analysis did not identify patient characteristics that would increase the risk of akathisia in patient receiving brexpiprazole for augmentation of antidepressants, but the following information should be appropriately provided to healthcare professionals: The incidence of akathisia was high at 2 mg/day in clinical studies; and generally, it occurs more frequently in the elderly.

Tardive dyskinesia that might be induced by the long-term use of brexpiprazole is highly difficult to treat, and the risk of the syndrome must therefore be minimized. Although no events of tardive dyskinesia were observed in the Japanese clinical studies (Studies 00058 and 00059) or foreign

[20)] Data for tabulation were extracted from non-Japanese and Japanese cases included in the [redacted]th Periodic Safety Update Reports on January 5, 2023 and July 22, 2022.

clinical studies,[10)11)] the event is known to occur in association with the long-term use of antipsychotics. Tardive dyskinesia just could not be detected in the clinical studies. Only the absence of the event in the clinical studies cannot rule out the risk of the event. The Japanese and foreign post-marketing information includes a certain number of adverse drug reaction reports on tardive dyskinesia, but at present, the applicant's discussion on these adverse drug reaction reports has not identified patient characteristics that may increase the risk of tardive dyskinesia in patients receiving brexpiprazole. Many attributes are reported as risk factors for tardive dyskinesia in published literature, and aging is considered as a certain risk factor, but no conclusion is reached on other patient characteristics as the risk factors (Manuals for Management of Individual Serious Adverse Drug Reactions – Dyskinesia, Ministry of Health, Labour and Welfare, May 2009 [revised in February 2022]). In addition, tardive dyskinesia associated with the use of antipsychotics have occurred in the non-elderly as well. In view of the above, use of brexpiprazole must be essentially minimized to reduce the risk of tardive dyskinesia.

Accordingly, the applicant is required to advise healthcare professionals that the dose of brexpiprazole, if used, and the duration of its use should be essentially minimized in consideration of the risk of extrapyramidal symptoms such as akathisia and tardive dyskinesia and to appropriately provide information about the incidence of akathisia in clinical studies (including its relatively high incidence in the elderly at 2 mg/day) and that about tardive dyskinesia included in the Manuals for Management of Individual Serious Adverse Drug Reactions. PMDA requested the applicant to take the above measures, and the applicant appropriately responded.

1.3 Clinical positioning

The following comments on the clinical positioning of brexpiprazole were raised from the expert advisors and PMDA's conclusion described in Section "7.R.4 Clinical positioning" of the Review Report (1) was supported by the expert advisors.

- In view of the guideline for treatment of depression used in Japan, the following PMDA's conclusion is appropriate: Brexpiprazole is positioned as one of the treatment options in patients who have inadequately responded to appropriate treatment with antidepressants and opt for the use of an atypical antipsychotic for augmentation of existing antidepressant therapy. In clinical practice, however, some medical institutions in Japan prefer augmentation of antidepressants with antipsychotics over options recommended in the guideline for treatment of depression, raising concerns that brexpiprazole may be carelessly used in patients including those who do not essentially need augmentation of antidepressants with antipsychotics. Measures should be taken to ensure that brexpiprazole is properly used.
- The guideline for treatment of depression used in Japan refers to not only new antidepressants such as SSRI, SNRI, and mirtazapine but also tricyclic antidepressants, etc. as the first-line drugs for treatment of moderate to severe depression and recommends selecting a different antidepressant among the above-listed drugs for non-responders to the first-line drug. In clinical settings, new antidepressants are mainly used as the first-line drugs, but there is evidence that tricyclic antidepressants are more effective than new antidepressants especially in patients with severe depression (*J Affect Disord.* 2000;58:19-36). For this reason, more than 1 course of appropriate treatment with antidepressants should be administered before the use of brexpiprazole is considered.

In addition, the Japanese guideline also states that antipsychotics should not precede other drugs for antidepressant augmentation therapy if multiple options are available for augmentation therapy. In view of the guideline's statements and discussion about the safety of brexpiprazole, healthcare professionals should carefully determine whether use of brexpiprazole for augmentation of antidepressants is appropriate, taking account of adverse reactions to brexpiprazole (extrapyramidal symptoms such as akathisia and tardive dyskinesia) and other treatment options. Such careful practice must be thoroughly implemented.

- The applicant should provide information about the antidepressants used concomitantly with brexpiprazole in clinical studies where the efficacy and safety of brexpiprazole were demonstrated and should also clearly state that no clinical studies have been conducted to assess the efficacy and safety of brexpiprazole as an add-on therapy to SSRI or SNRI versus tricyclic antidepressant monotherapy in patients with refractory depression.

PMDA requested the applicant to provide the package insert containing appropriate cautionary statement to the effect that healthcare professionals should carefully determine whether use of brexpiprazole for augmentation of antidepressants is appropriate, taking account of adverse reactions to brexpiprazole (extrapyramidal symptoms such as akathisia and tardive dyskinesia) and other treatment options, only for patients who had inadequate responses to multiple courses of appropriate treatment with antidepressants such as SSRI and SNRI. PMDA also requested the applicant to ensure the proper use of brexpiprazole by providing materials containing information on the treatment algorithm for antidepressants presented in the guideline for treatment of depression used in Japan and on the clinical positioning of brexpiprazole in this treatment algorithm. The applicant appropriately responded.

1.4 Indication

The following comments on the indications of brexpiprazole were raised from the expert advisors and PMDA's conclusion described in Section "7.R.5 Indication" of the Review Report (1) was supported by the expert advisors.

- Because patients with depressive state will not be eligible for treatment with brexpiprazole in view of clinical positioning of brexpiprazole as a drug for augmentation of antidepressants, "depressive state" should be removed from the proposed indications of brexpiprazole.
- Aripiprazole is already approved as a drug for augmentation of antidepressants, as intended with brexpiprazole, and it is indicated for "Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy)." This indication statement clearly defines patients eligible for treatment with aripiprazole by limiting to the patients with an inadequate response to existing antidepressant therapy. If the indication of brexpiprazole is different from that of aripiprazole although the two drugs have the same clinical positioning, healthcare professionals would be possibly confused. It is inevitable for PMDA conclude that the indication of brexpiprazole should be the same as that of aripiprazole.
- PMDA's conclusion that the "Indication" of brexpiprazole should be "Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy)" is acceptable, but measures should be taken to ensure the proper use of brexpiprazole, so that brexpiprazole would not be used carelessly at an early stage of the treatment of depression.

In view of the above, PMDA has concluded that the "Indication" of brexpiprazole should be specified as proposed by the applicant and requested the applicant to ensure the proper use of brexpiprazole, so that brexpiprazole would not be used carelessly at an early stage of the treatment of depression, for example, by providing the package insert containing a cautionary statement to the effect that healthcare professionals should carefully determine whether use of brexpiprazole for augmentation of antidepressants is appropriate. The applicant responded appropriately.

1.5 Dosage and administration

The following comments on the starting dose and recommended dose for the dosage and administration of brexpiprazole were raised from the expert advisors and PMDA's conclusion described in Section "7.R.6 Dosage and administration" of the Review Report (1) was supported by the expert advisors.

- Most of adverse events including akathisia occurred in an early stage of treatment with brexpiprazole, and the incidence of adverse events tended to increase with an increase in the dose of brexpiprazole. In view of these findings, the starting dose of 0.5 mg/day may be selected, as done in the US.
- PMDA has concluded that the starting dose of 1 mg/day is acceptable. PMDA's conclusion is appropriate because (i) the incidence of adverse events in foreign clinical studies (Studies 331-09-222 and 14570A) using the starting dose of 1 mg/day did not tend to be remarkably higher than that in foreign clinical studies (Studies 227, 228, and 214) using the starting dose of 0.5 mg/day; and (ii) Japanese clinical studies (Studies 00058 and 00059) using the starting dose of 1 mg/day only showed acceptable tolerability.
- On the basis of the submitted clinical study data on the efficacy and safety of brexpiprazole, PMDA's conclusion that the recommended dose of 1 mg/day should be specified in Japan is appropriate.

On the other hand, the expert advisors raised the following comments on the inclusion of the increased dose (2 mg/day) in the dosage and administration of brexpiprazole:

- The dose of 2 mg/day is not acceptable because (1) brexpiprazole may pose a risk of inducing tardive dyskinesia, which is difficult to treat; (2) the incidence of extrapyramidal symptoms such as akathisia tended to be higher in the 2 mg/day group than in the 1 mg/day group in the Japanese phase II/III study (Study 00058); and (3) an improvement in the symptom at 2 mg/day was not greater than that at 1 mg/day in Study 00058. Dose-adjustable drugs are easier for healthcare professionals to use, but even with this advantage, there is no evidence justifying the inclusion of the increased dose (2 mg/day) in the dosage and administration.
- While the guideline for treatment of depression used in Japan states that augmentation of antidepressants with antipsychotics should not precede other treatment options, antipsychotic augmentation is administered carelessly in the current clinical setting. The use of antipsychotics without careful consideration may pose a risk of inducing tardive dyskinesia in patients with depressive episodes that may be controllable with antidepressants including tricyclic ones. From a viewpoint of concerns about the risk of tardive dyskinesia, the increased dose (2 mg/day) is unacceptable.

- Because Study 00058 has demonstrated the efficacy of brexpiprazole 2 mg/day versus placebo, the increased dose (2 mg/day) may be included in the dosage and administration if there are patients medically eligible for an option of the dose increase.
- Although patients eligible for treatment with brexpiprazole 2 mg/day cannot be specifically characterized by their pathological conditions or from a viewpoint of its mechanism of action, brexpiprazole is intended to be used in patients with refractory depression, and thus use of the increased dose (2 mg/day) might be considered in routine clinical practice as long as the increased dose is tolerable in the patient. In view of a depression-specific pathology in which response to medication greatly varies from patient to patient, the increased dose (2 mg/day) may be allowed in patients who had an inadequate response to the initial dose if due attention is paid to the safety.
- In the current clinical practice in Japan, co-administration of brexpiprazole with antidepressants is seen in some cases. The dose of 2 mg/day may be used even if use of the increased dose (2 mg/day) in patients with MDD is not included in the dosage and administration.

PMDA's view based on comments raised from the expert advised in the Expert Discussion:
Although the patient population or pathological condition that can benefit from the increased dose (2 mg/day) cannot be specifically characterized, there is currently a certain medical need for additional options; some healthcare professionals want to increase the dose of brexpiprazole to 2 mg/day in patients who had a partial but inadequate response to 1 mg/day. Besides these situations, the incidence of adverse drug reactions was higher at 2 mg/day than at 1 mg/day, and patients eligible for the augmentation of antidepressants are those who are refractory to multiple courses of adequate antidepressant treatment. In summarizing the above, whether the efficacy of brexpiprazole at 2 mg/day is greater than that at 1 mg/day remains unclear, but brexpiprazole 2 mg/day has been demonstrated to be at least superior to placebo. PMDA has concluded, from a healthcare perspective, that the 2 mg/day dose may be included in the dosage and administration, and for the 2 mg/day dose to be used in clinical settings, the applicant should advise the following precautions to ensure that brexpiprazole is properly used as a drug for augmentation of antidepressants:

- In Study 00058, the efficacy of brexpiprazole in the 1 mg/day group is comparable to that in the 2 mg/day group, but the incidence of adverse drug reactions such as akathisia was higher in the 2 mg/day group than in the 1 mg/day group. The recommended dose is 1 mg/day in Japan, and the increased dose (2 mg/day) is not basically recommended. Healthcare professionals with a full understanding of the results of Study 00058 should carefully consider the necessity of increasing the dose of brexpiprazole to 2 mg. The necessity of increasing the dose of brexpiprazole to 2 mg, where applicable, should be carefully considered around 6 weeks after the start of treatment at 1 mg.
- The dose of brexpiprazole and the duration of its use should be essentially minimized in consideration of the risk of adverse reactions to this drug (extrapyramidal symptoms such as akathisia and tardive dyskinesia) for the following and other reasons: (i) The incidence of adverse drug reactions was higher in the 2 mg/day group than in the 1 mg/day group in Study 00058; and (ii) tardive dyskinesia with no useful predictors being available is known to occur in association with the long-term use of antipsychotics.
- Once the dose of brexpiprazole is increased to 2 mg, the patient should be more frequently monitored for any symptom, particularly adverse drug reactions such as extrapyramidal symptoms.

In the event of any adverse drug reaction, appropriate measures such as treatment discontinuation should be taken. The continued need for treatment with brexpiprazole 2 mg should be assessed at an interval of approximately 6 weeks even after the dose increase, and if the expected response is not achieved, the treatment should not be continued carelessly.

In view of the above conclusion, PMDA requested the applicant to specify the "Dosage and Administration" of brexpiprazole as described below, to include a cautionary statement to the above effect in the "Precautions Concerning Dosage and Administration" section of the package insert, and to provide information by disseminating materials containing considerations for determining the eligibility of patients for treatment with brexpiprazole, the dose, and the duration of treatment. The applicant appropriately responded.

Dosage and Administration

Schizophrenia:

The usual initial adult dosage is 1 mg of brexpiprazole orally administered once daily for at least 4 days, and then the dose should be increased to 2 mg orally administered once daily.

Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy):

The usual adult dosage is 1 mg of brexpiprazole orally administered once daily. The dose may be increased to 2 mg/day only in patients who are tolerant of the current dose and have an inadequate response to it.

(Underline denotes additions.)

1.6 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.7 Post-marketing investigations" of the Review Report (1). PMDA has concluded that the risk management plan (draft) for brexpiprazole should include the safety specifications presented in Table 25, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 26. Because tardive dyskinesia is an event that may occur in association with the long-term use of antipsychotics, the applicant should stay vigilant for possible occurrence of the event through routine pharmacovigilance activities using spontaneous reports and literature reports and consider measures to be taken promptly, where necessary.

Table 25. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Extrapyramidal symptoms <u>including akathisia</u> and tardive dyskinesia • Seizure • Dyslipidaemia (triglyceride, LDL cholesterol, HDL cholesterol, total cholesterol) • Neuroleptic malignant syndrome • Ileus paralytic • Rhabdomyolysis • Hyperglycaemia, diabetic ketoacidosis, and diabetic coma • Agranulocytosis and white blood cell decreased • Pulmonary embolism and deep vein thrombosis	• Suicidal behavior and suicidal ideation • Hypoglycaemia • Impulse-control disorder	None
Efficacy specification		
None		

(Underline denotes addition.)

Table 26. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)[a)]

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Disseminate information collected through early post-marketing phase vigilance • Develop and disseminate materials for healthcare professionals • Develop and disseminate materials for patients

a) Only additional pharmacovigilance activities and risk minimization activities relating to the present application

2. Overall Evaluation

As a result of its review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following condition. The present application is pertinent to a drug with a new indication and a drug with a new dosage, and the re-examination period for the indication and the dosage and administration in the present application is 4 years.

Indications

Schizophrenia

<u>Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy)</u>

(Underline denotes additions.)

Dosage and Administration

Schizophrenia:

The usual initial adult dosage is 1 mg of brexpiprazole orally administered once daily for at least 4 days, and then the dose should be increased to 2 mg orally administered once daily.

<u>Depression or depressive state (for use only in patients who have an inadequate response to existing antidepressant therapy):</u>

<u>The usual adult dosage is 1 mg of brexpiprazole orally administered once daily. The dose may be increased to 2 mg/day only in patients who are tolerant of the current dose but have an inadequate response to it.</u>

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

BMI	Body mass index
Brexpiprazole	Brexpiprazole
CGI-I	Clinical Global Impression - Improvement
desvenlafaxine	desvenlafaxine succinate hydrate
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
Duloxetine	Duloxetine hydrochloride
Escitalopram	Escitalopram oxalate
fluoxetine	fluoxetine hydrochloride
HAM-D	Hamilton Rating Scale for Depression
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
MADRS	Montgomery Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
Milnacipran	Milnacipran hydrochloride
MMRM	Mixed-model repeated measures
Paroxetine	Paroxetine hydrochloride hydrate
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality of Life
Quinidine	Quinidine gluconate
Rexulti	Rexulti Tablets 1 mg, Rexulti Tablets 2 mg, Rexulti OD Tablets 0.5 mg, Rexulti OD Tablets 1 mg, Rexulti OD Tablets 2 mg
Sertraline	Sertraline hydrochloride
SNRI	Serotonin-noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
Study 00058	Japanese phase II/III study (Study 331-102-00058)
Study 00059	Japanese long-term extension study (Study 331-102-00059)
Study 214	Study 331-13-214
Study 227	Study 331-10-227
Study 228	Study 331-10-228
$t_{1/2}$	Elimination Half-life
t_{max}	Time to Reach Maximum Concentration
Venlafaxine	Venlafaxine hydrochloride