Report on the Deliberation Results

June 11, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Trerief Tablets 25 mg
	Trerief OD Tablets 25 mg
Non-proprietary Name	Zonisamide (JAN*)
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	August 30, 2017

Results of Deliberation

In its meeting held on June 8, 2018, 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

May 16, 2018
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) Trerief Tablets 25 mg (b) Trerief OD Tablets 25 mg
Non-proprietary Name	Zonisamide
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	August 30, 2017
Dosage form/Strength	(a) Tablets, each containing 25 mg of Zonisamide (b) Orally-disintegrating tablets, each containing 25 mg of Zonisamide
Application Classification	Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage
Reviewing Office	Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of parkinsonism in patients with dementia with Lewy bodies (parkinsonism persisting even after treatment with levodopa-containing drugs), 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 indications and dosage and administration shown below, with the following condition. The incidences of hallucination, delusion, confusion, and delirium should be further investigated.

Indications

1. Parkinson's disease
   (for patients who did not respond adequately to a combination of levodopa-containing drugs and other antiparkinsonian drugs)
2. Parkinsonism in dementia with Lewy bodies
   (for patients with parkinsonism persistent even after treatment with levodopa-containing drugs)

(Underline denotes addition.)

Dosage and Administration

Zonisamide should be concomitantly administered with levodopa-containing drugs.

1. Parkinson's disease

The usual adult dosage is 25 mg of zonisamide administered orally once daily. For the improvement of the diurnal variation in the symptoms of Parkinson's disease (wearing-off phenomenon), 50 mg of zonisamide is administered orally once daily.

2. Parkinsonism in dementia with Lewy bodies

The usual adult dosage is 25 mg of zonisamide administered orally once daily.

(Underline denotes addition.)

Approval Condition

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

Attachment

Review Report (1)

March 2, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by PMDA.

Product Submitted for Approval

Brand Name	(a) Trerief Tablets 25 mg (b) Trerief OD Tablets 25 mg Trerief OD Tablets 50 mg
Non-proprietary Name	Zonisamide
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	August 30, 2017
Dosage form/Strength	(a) Tablets, each containing 25 mg of Zonisamide. (b) Orally-disintegrating tablets, each containing 25 or 50 mg of Zonisamide

Proposed Indications

1. Parkinson's disease (for patients who did not respond adequately to a combination of levodopa-containing drugs and other antiparkinsonian drugs)
2. Parkinsonism in dementia with Lewy bodies

(Underline denotes addition.)

Proposed Dosage and Administration

Zonisamide should be concomitantly administered with levodopa-containing drugs.

1. Parkinson's disease

The usual adult dosage is 25 mg of zonisamide administered orally once daily. For the improvement of the diurnal variation of the symptoms of Parkinson's disease (wearing-off phenomenon), 50 mg of zonisamide is administered orally once daily.

2. Parkinsonism in dementia with Lewy bodies

The usual adult dosage is 25 mg of zonisamide administered orally once daily. The oral dose may be increased to 50 mg once daily according to the patient's condition.

(Underline denotes addition.)

Table of Contents

List of Abbreviations

See Appendix.

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

Zonisamide is a 1,2-benzisoxazole derivative synthesized by Dainippon Pharmaceutical Co., Ltd. (currently Sumitomo Dainippon Pharma Co., Ltd.). In Japan, zonisamide was approved as an antiepileptic drug in 1989, and as an antiparkinsonian drug in 2009 with the 25 mg once-daily regimen. Then in 2013, zonisamide was approved for an additional indication of improvement of the diurnal variation of symptoms (wearing-off phenomenon) of Parkinson's disease (PD), with the 50 mg once-daily regimen. In foreign countries, zonisamide is approved only as an antiepileptic drug as of February 2018.

Dementia with Lewy bodies (DLB) is a dementia pathologically characterized by neuronal loss in the cerebrum and the brainstem and occurrence of many Lewy bodies which are α-synuclein-positive intracellular inclusion bodies, and shows parkinsonism as a major symptom. Parkinsonism in DLB is considered to be caused by the degeneration/loss of dopaminergic neuron in the substantia nigra as is the case with PD, and is qualitatively the same with PD-associated parkinsonism. Therefore, zonisamide was expected to be effective against parkinsonism in DLB as well, and clinical development was initiated in 20[redacted].

Recently, an application for a partial change was submitted to add "parkinsonism in DLB" in the indication and dosage regimen administration, based on the results of clinical studies conducted in Japan.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for addition of the new indication and new dosage, data relating to quality were not submitted.

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

3.1 Primary pharmacodynamics

3.1.1 Inhibition of currents of human T-type calcium channels Cav3.1 and Cav3.2, and sodium channels Nav1.1, Nav1.2, Nav1.3, and Nav1.6 (CTD 4.2.1.1.01)

Using HEK293 cells expressing human T-type calcium channel Cav3.1 or Cav3.2, the currents of Cav3.1 and Cav3.2 channels in the presence and in the absence of zonisamide 3 mmol/L were compared. Zonisamide 3 mmol/L inhibited Cav3.1 and Cav3.2 currents by 59.5% and 42.4%, respectively. In HEK293 cells expressing Cav3.1, zonisamide inhibited Cav3.1 current in a concentration-dependent manner, and 50% inhibitory concentration (IC_{50}) was 2408.1 μmol/L.

Using HEK293 cells expressing human-type sodium channel Nav1.1, Nav1.2, Nav1.3, or Nav1.6, currents of Nav1.1, Nav1.2, Nav1.3, and Nav1.6 channels were compared in the presence and in the absence of zonisamide 3 mmol/L. Zonisamide inhibited Nav1.1, Nav1.2, Nav1.3, and Nav1.6 currents by 12.6%, 10.7%, 11.9%, and 17.3%, respectively.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacological action of zonisamide:

In the pharmacology study conducted for the initial application for zonisamide, it was confirmed that zonisamide increases the dopamine level in the extracellular fluid of the striatum in combination with

levodopa, and inhibits monoamine oxidase (MAO) with relatively high selectivity for monoamine oxidase-B (MAO-B). However, the detailed molecular mechanism of zonisamide to improve motor dysfunction in patients with PD remains unclear. Abnormal neural activity in the subthalamic nucleus, which is considered as one of the causes of motor dysfunction in PD, is controlled by T-type calcium channels and sodium channels in the subthalamic nucleus, and the inhibition of T-type calcium channels is reported to improve motor dysfunction in a rat model of PD (e.g., *Pflugers Arch*. 2014;466:747-55, *J Neurosci*. 1999;19:7617-28). Therefore, in the present application, an *in vitro* study was conducted to investigate the inhibitory effect of zonisamide on human T-type calcium channels and sodium channels. Results showed that zonisamide inhibited both channels. These results suggest that, in addition to levodopa activation as has already been demonstrated, the inhibition of T-type calcium channels and sodium channels contributes to zonisamide's action to improve the motor dysfunction in patients with PD.

It is considered that DLB belongs to the same disease spectrum of Lewy body disease, as does PD, and shares common pathological features (occurrence of Lewy bodies), pathological conditions (degeneration/loss of dopamine neuron), and clinical symptom (parkinsonism) with PD (*Dementia with Lewy bodies*. first edition, Chugai-Igakusha; 2014:152), which suggests that zonisamide improves parkinsonism of DLB by the same mechanism as that which improves the motor dysfunction of PD.

PMDA's view:
The pharmacology studies conducted for the previous application presented data that suggest that the anti-PD effect of zonisamide is based on the effect on the dopamine neuron (see Review Report on "Trerief Tablets 25 mg" [November 12, 2008]). The newly conducted study demonstrated that zonisamide inhibits human T-type calcium channels and sodium channels which are possibly involved in the improvement of motor dysfunction of PD and parkinsonism in DLB. In addition, PD and DLB are considered to show similar disease conditions and pathological features, and parkinsonism in DLB is treated by the same drug therapy as that for PD in clinical setting (Clinical practice guideline for dementia). These findings suggest the possibility that zonisamide improves parkinsonism in DLB.

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

The non-clinical pharmacokinetic data were evaluated in support of the previous applications for Excegran (approved on March 31, 1989) and for Trerief (approved on January 21, 2009). The evaluated data were considered applicable to the present application for the new indication and dosage. Therefore, no additional data were submitted under this section.

5. Toxicology and Outline of the Review Conducted by PMDA

Since the present application is intended for addition of the new indication and new dosage, no additional toxicity data were 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

The biopharmaceutic data were evaluated in support of the previous applications for Excegran (approved on March 31, 1989) and for Trerief (approved on January 21, 2009). The evaluated data were considered applicable to the present application for the new indication and new dosage. Therefore, no additional data were submitted under this section.

6.2 Clinical pharmacology

Plasma zonisamide concentration was measured by high performance liquid chromatography (HPLC). The lower limit of quantitation was 0.0500 μg/mL.

Plasma concentration is expressed in mean or in mean ± standard deviation (SD), unless specified otherwise.

6.2.1 Study in patients

6.2.1.1 Japanese phase II study (Study D4404002, CTD 5.3.5.1.01)

Zonisamide (25 or 50 mg) was administered together with a combination drug containing levodopa and a peripheral Dopa decarboxylase inhibitor (levodopa/DCI combination drug) once daily to 97 patients with parkinsonism in DLB. Trough plasma concentration of zonisamide on Week 4 of administration was 1.43 ± 0.34 μg/mL (n = 39) and 3.43 ± 1.34 μg/mL (n = 37), respectively. Among the patients enrolled in the study, 47 patients (22 in the zonisamide 25 mg group, 25 in the zonisamide 50 mg group) and 16 patients (7, 9), respectively, received with donepezil hydrochloride and with Yokukansan (a herbal medicine), drugs expected to be administered in combination with zonisamide to patients with DLB. Neither of the concomitant drugs affected the trough concentration of zonisamide.

6.R Outline of the review conducted by PMDA

PMDA concluded that the clinical pharmacology data submitted for the present application do not pose any particular problem in the clinical use of zonisamide.

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

The applicant submitted data of 2 studies shown in Table 1 as the pivotal clinical study data on the efficacy and safety [for pharmacokinetics (PK), see Section “6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA”].

Table 1. Outline of the pivotal clinical studies

Data category	Region	Study	Phase	Study population	Number of randomized patients	Dosage regimen	Main endpoints
Evaluation	Japan	D4404002	II	Patients with parkinsonism in DLB	Placebo: 58 Zonisamide 25 mg: 51 Zonisamide 50 mg: 50	Oral administration of placebo or zonisamide 25 mg or 50 mg once daily.	Efficacy Safety PK
Evaluation	Japan	D4404013	III	Patients with parkinsonism in DLB	Double blind phase: Placebo: 120 Zonisamide 25 mg: 117 Zonisamide 50 mg: 114	Double blind phase: Oral administration of placebo or zonisamide 25 mg or 50 mg once daily.	Efficacy Safety
					Open-label phase: 307	Open-label phase: Oral administration of Zonisamide (25-50 mg) once daily (initial dose 25 mg).	

7.1 Japanese phase II study (Study D4404002, CTD 5.3.5.1.01, Study period ■ 20■ to ■ 20■)

A randomized, double-blind study was conducted to investigate the efficacy, safety, and PK of zonisamide (25 or 50 mg) in motor dysfunction of patients with parkinsonism in DLB (target sample size; 50 subjects per group, 150 subjects in total) in 60 study sites in Japan.

Placebo was administered during the 4-week run-in period, followed by once daily oral administration of placebo or zonisamide 25 mg or 50 mg during the 12-week treatment period. Levodopa/DCI combination drug and other anti-PD drugs were administered from 2 weeks before the start of the run-in period until the end of the treatment period, and anti-dementia drugs from 12 weeks before the start of the run-in period until the end of the treatment period, both without change in the dosage regimen.[1)]

The main inclusion criteria were patients aged ≥20 and <85 years who met all of the following:

- Diagnosis of probable DLB (almost certain clinically)[2)] according to the Clinical Diagnostic Criteria for DLB, ver. 3 (*Neurology*. 2005;65:1863-72)
- Unified Parkinson's disease rating scale (UPDRS) Part III total score ≥10
- Mini-mental state examination (MMSE) total score ≥10 and ≤26
- Receiving a levodopa/DCI combination drug for ≥12 weeks before the start of the run-in period

The study drug was administered to all of 159 randomized patients (58 in the placebo group, 51 in the zonisamide 25 mg group, and 50 in the zonisamide 50 mg group), and of these, 158 patients (58, 51, and 49), excluding 1 patient in the zonisamide 50 mg group whose raw data were lost by fire, were included in the safety analysis population. Of them, 152 patients (55, 48, and 49) with data of the UPDRS Part III total score both at baseline (before the start of the study drug administration in the treatment period) and after administration of the study drug for the treatment period were included in the modified intention-to-treatment (mITT) population, and handled as the primary efficacy analysis population. Study discontinuation occurred in 21 patients (5, 9, and 7). The main reasons for the discontinuation

1) If symptoms that are suspected to be caused by overstimulation of dopamine receptor (e.g., dyskinesia, psychiatric symptoms) occurred and were considered by the investigator (subinvestigator) to interfere with the study continuation, reducing the dose of anti-PD drugs was allowed, but increasing the once-reduced dose was prohibited.

2) The patient must have a "core feature" (progressive deterioration in cognitive functioning) as the absolute requirement. The patient also must meet (1) two or more of the "core features" (fluctuating cognition, recurrent visual hallucinations, or spontaneous [uninduced] parkinsonism) or (2) one of the "core features" and at least one of the "suggestive features" (REM sleep behavior disorder, marked sensitivity to neuroleptics, and low dopamine transporter uptake in the basal ganglia).

were adverse events in 14 patients (3, 5, and 6) and request for withdrawal from study participation (0, 4, and 1).

As for efficacy, Table 2 shows the change in the UPDRS Part III total score at Week 12 of administration (at the end of the treatment phase) from baseline, the primary endpoint. The between-group comparison showed a significant difference between the placebo group and the zonisamide 50 mg group ($P = 0.003$, analysis of covariance (ANCOVA) with treatment group as the fixed effect and baseline UPDRS Part III total score as the covariate), whereas no significant difference was observed between the placebo group and the zonisamide 25 mg group ($P = 0.099$) (adjusted for multiplicity of the test by Fisher's least significant difference [LSD] method).

Table 2. Change in UPDRS Part III total score at Week 12 from baseline (mITT)

	Placebo	Zonisamide 25 mg	Zonisamide 50 mg
Baseline (mean ± SD)	N = 55 31.4 ± 10.3	N = 48 33.2 ± 13.4	N = 49 32.4 ± 10.5
At week 12 (LOCF) (mean ± SD)	N = 55 29.3 ± 12.4	N = 48 28.8 ± 14.4	N = 49 26.2 ± 12.8
Change from baseline (LOCF) (least squares mean ± SE)[a]	−2.1 ± 0.9	−4.4 ± 1.0	−6.2 ± 1.0
Difference from placebo group in change (least squares mean [95% CI])[a]	-	−2.3 [−5.0, 0.4]	−4.1 [−6.8, −1.4]

a ANCOVA with treatment group as the fixed effect and baseline UPDRS Part III total score as the covariate

The changes in neuropsychiatric inventory (NPI)-10 total score and MMSE total score at Week 12 from baseline, the secondary endpoints, are shown in Tables 3 and 4, respectively.

Table 3. Changes in NPI-10 total score at Week 12 from baseline (mITT)

	Placebo	Zonisamide 25 mg	Zonisamide 50 mg
Baseline (mean ± SD)	N = 52 7.6 ± 8.5	N = 45 6.4 ± 8.7	N = 46 7.8 ± 8.3
At week 12 (LOCF) (mean ± SD)	N = 52 7.4 ± 10.6	N = 45 7.7 ± 10.2	N = 46 7.8 ± 6.7
Change from baseline (LOCF) (least squares mean ± SE) [a]	0.0 ± 1.0	1.1 ± 1.1	0.1 ± 1.1
Difference from placebo group in change (least squares mean [95% CI])[a]	-	1.1 [−1.8, 4.0]	0.2 [−2.7, 3.0]

a ANCOVA with treatment group as the fixed effect and baseline total NPI-10 score as the covariate

Table 4. Change in MMSE total score at Week 12 from baseline (mITT)

	Placebo	Zonisamide 25 mg	Zonisamide 50 mg
Baseline (mean ± SD)	N = 54 21.4 ± 4.74	N = 44 22.1 ± 5.3	N = 45 21.2 ± 3.9
At week 12 (LOCF) (mean ± SD)	N = 54 21.1 ± 6.2	N = 44 21.8 ± 5.7	N = 45 21.8 ± 4.2
Change from baseline (LOCF) (least squares mean ± SE)[a]	−0.4 ± 0.4	−0.3 ± 0.4	0.5 ± 0.4
Difference from placebo group in change (least squares mean [95% CI])[a]	-	0.1 [−1.1, 1.3]	0.9 [−0.3, 2.1]

a ANCOVA with treatment group as the fixed effect and baseline MMSE total score as the covariate

As for safety, the incidence of adverse events was 50.0% (29 of 58) in the placebo group, 43.1% (22 of 51) in the zonisamide 25 mg group, and 65.3% (32 of 49) in the zonisamide 50 mg group. Table 5 shows main events.

Table 5. Incidence of main adverse events (safety analysis population)

	Placebo (N = 58)	Zonisamide 25 mg (N = 51)	Zonisamide 50 mg (N = 49)
Nasopharyngitis	6.9 (4)	9.8 (5)	10.2 (5)
Weight decreased	0 (0)	2.0 (1)	8.2 (4)
Excoriation	0 (0)	0 (0)	6.1 (3)
Decreased appetite	1.7 (1)	3.9 (2)	6.1 (3)
Contusion	8.6 (5)	5.9 (3)	2.0 (1)

% (number of patients)

No death occurred. Serious adverse events were observed in 3 patients in the placebo group (volvulus, forearm fracture, and anxiety disorder), 4 patients in the zonisamide 25 mg group (dysphagia/pneumonia aspiration, lung adenocarcinoma, pneumonia, and rectal cancer), and 3 patients in the zonisamide 50 mg group (back pain, ileus, and decreased appetite/chondrocalcinosis pyrophosphate). A causal relationship to the study drug could not be ruled out for decreased appetite in the zonisamide 50 mg group.

Adverse events leading to discontinuation of the study drug occurred in 2 patients in the placebo group (volvulus and anxiety disorder), 5 patients in the zonisamide 25 mg group (somnolence, abdominal pain upper/dysgeusia, drug eruption, lung adenocarcinoma, and pneumonia), and 6 patients in the zonisamide 50 mg group (back pain, hallucination, ileus, cognitive disorder, rash, and decreased appetite).

7.2 Japanese phase III study (Study D4404013, CTD 5.3.5.1.02, Study period [redacted] 20[redacted] to [redacted] 20[redacted])

A clinical study consisting of a randomized, double-blind period (double-blind period) and an open-label, uncontrolled period (open-label period) was conducted to investigate the efficacy and the safety of zonisamide (25 and 50 mg) in motor dysfunction of patients with parkinsonism in DLB (target sample size; 100 subjects per group, 300 subjects in total) at 109 study sites in Japan.

Placebo was administered during the 4-week run-in period, followed by once daily oral administration of placebo, zonisamide 25 mg, or zonisamide 50 mg during the succeeding 12-week double-blind period. In the open-label period (40 weeks) which started after the end of the double-blind period, zonisamide was administered once daily at the initial dose of 25 mg, and the dose could be adjusted to 25 or 50 mg as appropriate at the discretion of the investigator (or subinvestigator). Once the dose of zonisamide was changed during the open-label period, no further change was to be made for at least 2 weeks. Levodopa/DCI combination drug and other anti-PD drugs were administered from 2 weeks before the start of the run-in period until the end of the open-label period, and anti-dementia drugs from 12 weeks before the start of the run-in period until the end of the open-label period, both without change in the dosage regimen.[1)]

The main inclusion criteria were patients aged ≥20 and <90 years who met all of the following:

- Diagnosis of "probable DLB (almost certain clinically)[2)] according to the Clinical Diagnostic Criteria for DLB, ver. 3 (*Neurology*. 2005;65:1863-72)
- UPDRS Part III total score ≥10
- MMSE total score ≥10
- Receiving a levodopa/DCI combination drug for ≥12 weeks before the start of the run-in period

(a) Double-blind period

The study drug was administered to 350 patients (120 in the placebo group, 117 in the zonisamide 25 mg group, and 113 in the zonisamide 50 mg group) out of 351 randomized patients (120, 117, and 114). Of them, 346 patients (118, 117, and 111) with data of UPDRS Part III total score both at baseline (before the start of the study drug administration in the double-blind period) and after administration of the study drug were included in mITT population, and handled as the primary efficacy analysis population. Among the 350 patients who received the study drug, 1 patient randomized to the zonisamide 50 mg group received placebo by mistake. As a result, the safety analysis population included 350 patients (121, 117, and 112). During the double-blind period, study discontinuation occurred in 31 patients (11, 5, and 15). The main reasons for the discontinuation were adverse events in 22 patients (6, 5, and 11) and request for withdrawal from study participation in 5 patients (2, 0, and 3).

As for efficacy, Table 6 shows the change in UPDRS Part III total score at Week 12 of administration from baseline, the primary endpoint. A significant difference was observed both between the placebo group and the zonisamide 25 mg group and between the placebo group and the zonisamide 50 mg group ($P = 0.005$, $P = 0.005$; mixed model for repeated measures [MMRM] with treatment groups, evaluation time points [Weeks 4, 8, and 12], study sites, and interaction between treatment groups and evaluation time points as fixed effects, and baseline UPDRS Part III total score as the covariate, adjusted for multiplicity of the test by Hochberg method).

Table 6. Change in UPDRS Part III total score at Week 12 from baseline (mITT)

	Placebo	Zonisamide 25 mg	Zonisamide 50 mg
Baseline (mean ± SD)	N = 118 30.5 ± 10.8	N = 117 31.9 ± 12.1	N = 111 31.2 ± 12.4
At Week 12 (mean ± SD)	N = 110 28.9 ± 12.6	N = 110 27.2 ± 11.9	N = 99 27.0 ± 12.7
Change from baseline (least squares mean ± SE)[a]	−1.4 ± 0.6	−4.1 ± 0.6	−4.0 ± 0.7
Difference from placebo group in change (least squares mean [95% CI])[a]	-	−2.7 [−4.4, −0.9]	−2.6 [−4.4, −0.8]

a MMRM with treatment group, evaluation time point [Week 4, Week 8, and Week 12], study site, and interaction between treatment group and evaluation time point as fixed effects, and baseline UPDRS Part III total score as the covariate

The changes in total NPI-10 score and MMSE total score at Week 12 from baseline, the secondary endpoints, are shown in Tables 7 and 8, respectively.

Table 7. Changes in total NPI-10 score at Week 12 from baseline (mITT)

	Placebo	Zonisamide 25 mg	Zonisamide 50 mg
Baseline (mean ± SD)	N = 114 6.2 ± 7.6	N = 113 7.0 ± 10.1	N = 110 6.0 ± 7.2
At Week 12 (LOCF) (mean ± SD)	N = 114 6.9 ± 8.9	N = 113 6.7 ± 11.1	N = 110 6.0 ± 7.8
Change from baseline (least squares mean ± SE)[a]	0.6 ± 0.6	−0.2 ± 0.6	−0.1 ± 0.6
Difference from placebo group in change (least squares mean [95% CI])[a]	-	−0.9 [−2.6, 0.9]	−0.7 [−2.5, 1.0]

a ANCOVA with treatment group and study site as the fixed effects and baseline total NPI-10 score as the covariate

Table 8. Changes in MMSE total score at Week 12 from baseline (mITT)

	Placebo	Zonisamide 25 mg	Zonisamide 50 mg
Baseline (mean ± SD)	N = 114 22.6 ± 5.2	N = 113 21.0 ± 5.7	N = 110 22.0 ± 5.1
At Week 12 (LOCF) (mean ± SD)	N = 114 22.4 ± 5.3	N = 113 20.7 ± 6.1	N = 110 21.2 ± 5.7
Change from baseline (least squares mean ± SE)[a]	0.0 ± 0.3	−0.3 ± 0.3	−0.8 ± 0.3
Difference from placebo group in change (least squares mean [95% CI])[a]	-	−0.3 [−1.0, 0.5]	−0.8 [−1.5, −0.1]

a ANCOVA with treatment group and study site as the fixed effects and baseline MMSE total score as the covariate

As for safety, the incidence of adverse events was 47.1% (57 of 121) in the placebo group, 48.7% (57 of 117) of patients in the zonisamide 25 mg group, and 54.5% (61 of 112) in the zonisamide 50 mg group. Table 9 shows main events.

Table 9. Incidence of main adverse events (safety analysis population)

	Placebo (N = 121)	Zonisamide 25 mg (N = 117)	Zonisamide 50 mg (N = 112)
Nasopharyngitis	5.8 (7)	6.0 (7)	9.8 (11)
Decreased appetite	0.8 (1)	3.4 (4)	7.1 (8)
Constipation	4.1 (5)	0 (0)	3.6 (4)
Fall	3.3 (4)	2.6 (3)	3.6 (4)
Contusion	4.1 (5)	5.1 (6)	1.8 (2)
Somnolence	0.8 (1)	4.3 (5)	0.9 (1)
Hypokalaemia	3.3 (4)	0.9 (1)	0 (0)

% (number of patients)

Death occurred in 1 patient in the zonisamide 25 mg group (myocardial ischaemia) and in 1 patient in the zonisamide 50 mg group (drowning). A causal relationship to the study drug was ruled out for both events. No death occurred in the placebo group.

Serious adverse events were observed in 10 patients in the placebo group (femur fracture, oesophageal injury/pneumonia aspiration, spinal compression fracture, femoral neck fracture, back pain, cardiac failure acute, pneumonia, altered state of consciousness, transient ischaemic attack, and parkinsonism), 7 patients in the zonisamide 25 mg group (pneumonia in 2, myocardial ischaemia, femoral neck fracture, large intestine polyp, psychiatric symptom, and abnormal behavior in 1 each), and 7 patients in the zonisamide 50 mg group (pneumonia, dehydration, drowning, tooth impacted/benign bone neoplasm, tibia fracture, duodenal ulcer, and B-cell lymphoma). A causal relationship to the study drug could not be ruled out for parkinsonism in the placebo group and for psychiatric symptoms in the zonisamide 25 mg group.

Adverse events leading to discontinuation of the study drug were observed in 6 patients in the placebo group (femur fracture, psychiatric symptom, femoral neck fracture, cardiac failure acute, pneumonia, and parkinsonism), 6 patients in the zonisamide 25 mg group (myocardial ischaemia, dementia with Lewy bodies, femoral neck fracture, psychiatric symptom, somnolence, and attention deficit/hyperactivity disorder), and 11 patients in the zonisamide 50 mg group (decreased appetite in 2, fall, visual hallucination/decreased appetite, renal dysfunction/blood creatine phosphokinase increased/crush syndrome/decubitus ulcer/dehydration/pneumonia, drowning, psychiatric symptom, tibia fracture, drug eruption, B-cell lymphoma, and spinal compression fracture in 1 each).

(b) Open-label period

Among 319 patients who completed the double-blind period (109 in the placebo group, 112 in the zonisamide 25 mg group, and 98 in the zonisamide 50 mg group [treatment groups in the double-blind period]), 307 patients (106, 106, and 95) proceeded to the open-label period. One patient in the placebo group received zonisamide 50 mg once daily from the start of the open-label period by the mistake of both the patient and the caretaker. During the open-label period, study discontinuation occurred in 77 patients (24, 25, and 28). The main reasons for the discontinuation were adverse events in 48 patients (18, 12, and 18) and request for withdrawal from study participation in 18 patients (4, 8, and 6).

During the open-label period, the dose of zonisamide was increased to 50 mg in 187 patients (64, 68, and 55), and the increased dose was maintained up to Week 52 in 136 patients (47, 51, and 38).

A total of 335 randomized patients (106, 117, and 112) who received at least 1 dose of zonisamide in the double-blind or open-label period were included in the long-term population (LT) and subjected to the analysis of safety and efficacy.

As for efficacy, Table 10 shows the changes over time in UPDRS Part III total score.

Table 10. Changes over time in UPDRS Part III total score (LT)

	Placebo			Zonisamide 25 mg			Zonisamide 50 mg		
	No. of patients	Score	Change[a]	No. of patients	Score	Change[b]	No. of patients	Score	Change[b]
Baseline	-	-	-	117	31.9 ± 12.1	-	112	31.2 ± 12.3	-
Week 12	106	28.6 ± 12.6	-	111	27.2 ± 11.9	−4.2 ± 7.0	99	27.0 ± 12.7	−4.6 ± 6.5
Week 28	93	25.1 ± 12.6	−2.9 ± 5.6	99	25.9 ± 12.8	−5.1 ± 7.3	80	24.3 ± 11.1	−6.3 ± 8.2
Week 52	81	24.9 ± 13.8	−2.8 ± 7.8	81	25.6 ± 12.1	−5.4 ± 9.3	67	25.1 ±12.7	−6.0 ± 8.9

Mean ± SD
Each evaluation time point indicates weeks from the start of the double-blind period.
a Change from Week 12; b Change from baseline

As for safety, the safety since the start of zonisamide administration[3)] was evaluated as the long-term safety. The incidence of adverse events was 82.1% (87 of 106) in the placebo group, 89.7% (105 of 117) in the zonisamide 25 mg group, and 86.6% (97 of 112) in the zonisamide 50 mg group. Table 11 shows main adverse events.

3) Open-label period in the placebo group. Double-blind period and open-label period in the zonisamide 25 mg and 50 mg groups.

Table 11. Incidence of main adverse events (LT)

	Placebo (N = 106)	Zonisamide 25 mg (N = 117)	Zonisamide 50 mg (N = 112)
Nasopharyngitis	15.1 (16)	23.1 (27)	21.4 (24)
Contusion	14.2 (15)	9.4 (11)	8.0 (9)
Weight decreased	6.6 (7)	8.5 (10)	8.0 (9)
Decreased appetite	3.8 (4)	9.4 (11)	7.1 (8)
Fall	6.6 (7)	6.8 (8)	7.1 (8)
Constipation	6.6 (7)	3.4 (4)	7.1 (8)
Somnolence	6.6 (7)	7.7 (9)	4.5 (5)
Decubitus ulcer	4.7 (5)	2.6 (3)	4.5 (5)
Diarrhoea	3.8 (4)	2.6 (3)	4.5 (5)
Oedema peripheral	0.9 (1)	0 (0)	4.5 (5)
Influenza	2.8 (3)	6.0 (7)	3.6 (4)
Back pain	3.8 (4)	4.3 (5)	3.6 (4)
Pneumonia	0.9 (1)	3.4 (4)	3.6 (4)
Pneumonia aspiration	2.8 (3)	2.6 (3)	3.6 (4)
Cystitis	3.8 (4)	1.7 (2)	3.6 (4)
Anaemia	0 (0)	1.7 (2)	3.6 (4)
Spinal compression fracture	5.7 (6)	1.7 (2)	3.6 (4)
Arthralgia	1.9 (2)	1.7 (2)	3.6 (4)
Dehydration	9.4 (10)	7.7 (9)	2.7 (3)
Insomnia	1.9 (2)	3.4 (4)	2.7 (3)
Bronchitis	5.7 (6)	5.1 (6)	1.8 (2)
Psychiatric symptom	0.9 (1)	4.3 (5)	1.8 (2)
Dental caries	0.9 (1)	8.5 (10)	0.9 (1)

% (number of patients)

During the open-label period, death occurred in 3 patients in the placebo group (subarachnoid haemorrhage, pneumonia aspiration, and cerebral infarction), 3 patients in the zonisamide 25 mg group (subarachnoid haemorrhage, drowning, and pulmonary embolism), and 1 patient in zonisamide 50 mg group (cardiac death). A causal relationship to the study drug was ruled out for all of them.

During the open-label period, serious adverse events were observed in 21 patients in the placebo group, 16 patients in the zonisamide 25 mg group, and 18 patients in the zonisamide 50 mg group. Main serious adverse events were urinary tract infection, femoral neck fracture, spinal compression fracture, dehydration, pneumonia aspiration, and cardiac failure (2 patients each) in the placebo group, pneumonia aspiration (2 patients) in the zonisamide 25 mg group, and pneumonia aspiration (4 patients), cataract operation, influenza, and subdural haematoma (2 patients each) in the zonisamide 50 mg group. A causal relationship to the study drug could not be ruled out for pneumonia aspiration in 1 patient in the zonisamide 50 mg group.

During the open-label period, adverse events leading to discontinuation of the study drug were observed in 18 patients in the placebo group, 12 patients in the zonisamide 25 mg group, and 18 patients in the zonisamide 50 mg group. Main adverse events leading to discontinuation of the study drug were somnolence (3 patients), and femoral neck fracture and spinal compression fracture (2 patients each) in the placebo group, pneumonia aspiration (2 patients) in the zonisamide 25 mg group, and pneumonia aspiration (3 patients) in the zonisamide 50 mg group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of zonisamide in the treatment of parkinsonism in DLB:

Currently, there are no therapeutic drugs approved in Japan for the indication for parkinsonism in DLB, and the disease is treated by the same drug therapy as used for PD. The clinical practice guideline for dementia recommends levodopa for the treatment of parkinsonism in DLB. However, DLB is less responsive than PD to levodopa, and because increasing the dose of levodopa is more likely to cause aggravation of behavioral and psychological symptoms of dementia (BPSD) and delirium in patients with DLB than in patients with PD, the guideline advises increasing the dose of levodopa gradually beginning from a low level and controlling the dose at the lowest necessary dose. Although dopamine agonists are sometimes concomitantly administered with levodopa, dopamine agonists require caution against BPSD aggravation and delirium than does levodopa. Amantadine and anticholinergic drugs are not usually used because they cause delirium and possibly decrease cognitive function (*Journal of clinical and experimental medicine*. 2011;236:987-91, Clinical practice guideline for dementia). Thus, the options for drug therapy of parkinsonism in DLB are extremely limited, calling for a therapeutic drug that does not cause the aggravation of BPSD and delirium.

Zonisamide is a levodopa-activating anti-PD drug and, in Japan, it is approved as a drug to be used in patients who had not responded sufficiently to combinations of levodopa-containing drugs and other anti-PD drugs. As described above, anti-PD drugs other than levodopa are not aggressively used for the patient with DLB. In contrast, zonisamide is positioned as a drug to be administered in order to further improve parkinsonism in DLB in patients who are being treated with levodopa-containing drugs.

In the clinical studies conducted for the present application involving patients with parkinsonism in DLB who were taking levodopa/DCI combination drug, efficacy of zonisamide against parkinsonism in DLB was demonstrated [see Section "7.R.2 Efficacy"], and the risk of BPSD aggravation and delirium caused by zonisamide was similar to that by placebo [see Section "7.R.3 Safety"]. Taking account of the fact that there are no reports of placebo-controlled, randomized studies in patients with parkinsonism in DLB, zonisamide, a drug with efficacy and safety confirmed by clinical studies, is expected to provide a new treatment option as a drug to be used in combination with levodopa-containing drugs in the treatment of parkinsonism in DLB.

PMDA's view:

The clinical practice guideline for dementia recommends the use of levodopa for parkinsonism in DLB in a similar manner as for the treatment of PD, but the guideline recommends using levodopa at low doses in order to avoid the risk of aggravation of psychiatric symptom. Also, the guideline does not recommend the aggressive use of anti-PD drugs such as anticholinergic drugs and dopamine agonists because of the risk of decline in cognitive function and aggravation of psychiatric symptom. Zonisamide is not mentioned in the clinical practice guideline for dementia. However, under the above situations, zonisamide may be positioned as a drug to be concomitantly administered with levodopa-containing drugs in the treatment of parkinsonism in DLB for patients with persisting parkinsonism despite the use of levodopa-containing drugs for a certain period, for the following reasons: (1) In the clinical studies

in patients with DLB, zonisamide demonstrated the efficacy and safety in combination with levodopa-containing drugs in patients with DLB with persisting parkinsonism despite treatment with levodopa-containing drugs for a certain period, and (2) zonisamide has a levodopa-activating effect.

7.R.2 Efficacy

The applicant's explanation about the efficacy of zonisamide against parkinsonism in DLB:
The clinical symptoms of parkinsonism in DLB are similar to those of PD (*Dementia with Lewy bodies*. first edition, Chugai-Igakusha; 2014:7). Therefore, UPDRS Part III (Japanese version: *Neurological therapeutics*. 2000;17:577-91), the parameter confirmed to be reliable and appropriate as the endpoint for motor functions of PD, was used as the primary endpoint that would appropriately evaluate the efficacy against parkinsonism in DLB.

The changes in the UPDRS Part III total score at Week 12 from baseline in the placebo-controlled studies[4)] on DLB are shown in Tables 2 and 6. Significant improvement was observed in the zonisamide 50 mg group in the phase II study and in the zonisamide 25 and 50 mg groups in the phase III study compared with the placebo group. There are no study reports of clinically significant changes in UPDRS Part III total score in patients with DLB. However, according to the report of a placebo-controlled, double-blind study on rasagiline in patients with PD, the clinically significant minimum change in UPDRS Part III total score is −2.0 to −2.4, based on the comparison with the overall improvement (*Movement Disorders*. 2011;26:813-8). The clinical significance of the improvement of motor function to an extent similar or better than that observed in patients with PD is clear, taking account of the following: (1) The difference of the change in UPDRS Part III total score between the zonisamide groups and the placebo group (−2.7 in the zonisamide 25 mg group, −2.6 in the zonisamide 50 mg group) observed in the phase III study in patients with DLB was similar to, or greater than, the difference reported in patients with PD, (2) the effect of levodopa in DLB is generally inferior to that in PD (Clinical practice guideline for dementia), and (3) motor function deteriorates more rapidly in patients with DLB than in patients with PD (*J Neurol Neurosurg Psychiatry*. 2006;77:585-9).

The phase III study demonstrated that the efficacy of zonisamide lasts up to Week 52 of administration.

Based on the above, the applicant considers that zonisamide 25 mg and 50 mg are effective against parkinsonism in DLB.

PMDA's view:
Although the index for efficacy evaluation has not been established in the treatment of parkinsonism in n DLB, there is a certain validity in using the UPDRS Part III total score as the primary endpoint, taking account of the explanation of the applicant. In the confirmatory phase III study which was designed based on the results of the phase II study, the zonisamide 25 mg and 50 mg groups were shown to be superior to the placebo group in this primary endpoint. Therefore, zonisamide 25 mg and 50 mg have been shown to be effective against parkinsonism in DLB. However, since the change in the UPDRS Part III total score in the zonisamide 25 mg and 50 mg groups in the phase III study was similar with each

4) Phase II study and phase III study (double-blind period)

other, appropriateness of including 50 mg in addition to 25 mg to the dosage regimen is further discussed in Section "7.R.5 Dosage and administration."

7.R.3 Safety

PMDA asked the applicant to compare the safety profile of zonisamide between patients with DLB and patients with PD, and to explain whether there are adverse events requiring particular caution in patients with DLB.

The applicant's response:

In the clinical studies in patients with DLB or PD, the incidences of death, serious adverse events, and adverse events leading to discontinuation of the study drug are as shown below. Table 12 shows the incidence of adverse events in the placebo-controlled studies in patients with DLB or PD. There was no significant difference in the incidence of adverse events, serious adverse events, or adverse events leading to discontinuation of the study drug between the study on patients with DLB and the study on patients with PD. Comparison of the incidence of individual events showed a higher incidence of decreased appetite in zonisamide 50 mg of the study on DLB compared with the study on PD, whereas no significant change was observed for other events.

Table 12. Incidence of adverse events in placebo-controlled study in patients with DLB or PD (safety analysis population)

	DLB[a]			PD[b]		
	Placebo (N = 179)	Zonisamide 25 mg (N = 168)	Zonisamide 50 mg (N = 161)	Placebo (N = 309)	Zonisamide 25 mg (N = 272)	Zonisamide 50 mg (N = 310)
Adverse events	48.0 (86)	47.0 (79)	57.8 (93)	60.5 (187)	61.0 (166)	65.8 (204)
Adverse events resulting in death	0 (0)	0.6 (1)	0.6 (1)	0 (0)	0.4 (1)	0.3 (1)
Myocardial ischaemia	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Drowning	0 (0)	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)
Sudden death	0 (0)	0 (0)	0 (0)	0 (0)	0.4 (1)	0 (0)
Completed suicide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.3 (1)
Serious adverse events	7.3 (13)	6.5 (11)	6.2 (10)	1.9 (6)	4.4 (12)	4.2 (13)
Pneumonia	0.6 (1)	1.8 (3)	0.6 (1)	0 (0)	0.7 (2)	0 (0)
Granulocyte count decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.0 (3)
Pyrexia	0 (0)	0 (0)	0 (0)	0.6 (2)	0.4 (1)	0 (0)
Cellulitis	0 (0)	0 (0)	0 (0)	0 (0)	0.7 (2)	0 (0)
Adverse events leading to discontinuation of the study drug	4.5 (8)	6.5 (11)	10.6 (17)	3.2 (10)	3.7 (10)	7.4 (23)
Decreased appetite	0 (0)	0 (0)	2.5 (4)	0 (0)	0.4 (1)	0.3 (1)
Hallucination	0 (0)	0 (0)	0.6 (1)	0 (0)	0.7 (2)	0.6 (2)
Somnolence	0 (0)	1.2 (2)	0 (0)	0 (0)	0 (0)	1.0 (3)
Nausea	0 (0)	0 (0)	0 (0)	0.3 (1)	0 (0)	1.0 (3)
Pyrexia	0 (0)	0 (0)	0 (0)	0.6 (2)	0.4 (1)	0 (0)
Dysaesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.6 (2)

% (number of patients)
a Phase II study and phase III study (double-blind period) combined
b Studies AD810N-202-1, AD810N-204-5, AD810N-303-8, and D44021001 combined.

Table 13 shows the incidence of adverse events in the long-term treatment studies conducted in patients with DLB or PD. No significant difference was observed in the long-term safety profile.

Table 13. Incidence of adverse events in the long-term treatment study in patients with DLB or PD (safety analysis population)

	DLB[a] (N = 335)	PD[b] (N = 136)
Adverse events	86.3 (289)	92.6 (126)
Adverse events resulting in death	3.0 (10)	0.7 (1)
Subarachnoid haemorrhage	0.6 (2)	0 (0)
Drowning	0.6 (2)	0 (0)
Serious adverse events	21.5 (72)	11.0 (15)
Pneumonia aspiration	2.4 (8)	0 (0)
Pneumonia	1.5 (5)	1.5 (2)
Femoral neck fracture	1.5 (5)	0.7 (1)
Spinal compression fracture	1.2 (4)	0 (0)
Dehydration	1.2 (4)	0 (0)
Influenza	0.9 (3)	0 (0)
Cardiac failure	0.6 (2)	0 (0)
Dysphagia	0.6 (2)	0 (0)
Drowning	0.6 (2)	0 (0)
Urinary tract infection	0.6 (2)	0 (0)
Subdural haematoma	0.6 (2)	0 (0)
Subarachnoid haemorrhage	0.6 (2)	0 (0)
Prostate cancer	0.6 (2)	0 (0)
Psychiatric symptom	0.6 (2)	0 (0)
Asphyxia	0.6 (2)	0 (0)
Cataract operation	0.6 (2)	0 (0)
Adverse events leading to study drug discontinuation or dose reduction	23.0 (77)	22.8 (31)
Pneumonia aspiration	1.8 (6)	0 (0)
Decreased appetite	1.5 (5)	2.9 (4)
Somnolence	1.5 (5)	2.2 (3)
Weight decreased	1.2 (4)	1.5 (2)
Femoral neck fracture	1.2 (4)	0.7 (1)
Spinal compression fracture	1.2 (4)	0 (0)
Hallucination	0.9 (3)	2.9 (4)
Dementia with Lewy bodies	0.9 (3)	0 (0)
Psychiatric symptom	0.9 (3)	0 (0)
Hallucination, visual	0.6 (2)	0 (0)
Drowning	0.6 (2)	0 (0)
Subarachnoid haemorrhage	0.6 (2)	0 (0)
Dehydration	0.6 (2)	0 (0)
Prostate cancer	0.6 (2)	0 (0)
Cerebral infarction	0.6 (2)	0 (0)
Drug eruption	0.6 (2)	0 (0)

% (number of patients)
a After the start of zonisamide administration in the phase III study; b Studies AD810N-203-2 and AD810N-302-6 combined

Below are described the results of investigations on the effect of zonisamide on psychiatric symptom, cognitive function, appetite, and body weight, parameters possibly affected by zonisamide in patients with DLB, as well as on the effect of concomitant drugs on these parameters.

(a) Effect on psychiatric symptom

Taking account of the facts that, in patients with DLB, treatment with levodopa may aggravate psychiatric symptoms (*Neurology*. 2017;89:1-13) and that zonisamide has a levodopa-activating effect (*Epilepsy Res*. 1995;22:193-205), the effect of zonisamide on psychiatric symptoms was evaluated by NPI-10. Tables 3 and 7 show the change in total NPI-10 score at Week 12 from baseline in the placebo-controlled studies in patients with DLB. There was little change in total NPI-10 score in any group.

Table 14 shows the incidence of adverse events related to psychiatric disorder in clinical studies in patients with DLB. In the placebo-controlled study, there was no significant difference in the incidence

between the placebo group and zonisamide groups. The events observed in the long-term treatment study were similar to those observed in the placebo-controlled study.

Table 14. Incidence of adverse events[a] related to psychiatric disorder in clinical studies (safety analysis population)

	Placebo-controlled study[b]			Long-term treatment study[c] (N = 335)
	Placebo (N = 179)	Zonisamide 25 mg (N = 168)	Zonisamide 50 mg (N = 161)	
Adverse events related to psychiatric disorder	4.5 (8)	6.0 (10)	4.3 (7)	13.4 (45)
Psychiatric symptom	1.1 (2)	1.2 (2)	0.6 (1)	2.4 (8)
Hallucination	0.6 (1)	0.6 (1)	1.2 (2)	1.8 (6)
Insomnia	0.6 (1)	1.2 (2)	0.6 (1)	2.7 (9)
Delusion	1.1 (2)	0 (0)	0 (0)	0.3 (1)
Serious adverse events	0.6 (1)	1.2 (2)	0 (0)	1.5 (5)
Adverse events leading to discontinuation of the study drug	1.1 (2)	1.2 (2)	1.9 (3)	2.1 (7)

% (number of patients)

a Preferred terms (PTs) classified as "Psychiatric disorders" in the System Organ Class of Medical Dictionary for Regulatory Activities (MedDRA SOC)

b Phase II study and phase III study (double-blind period) combined

c After the start of zonisamide administration in phase III study

In the phase III study in patients with DLB, suicide attempt occurred in 1 patient (zonisamide 50 mg group) after the end of administration of the study drug, but a causal relationship to the study drug was ruled out.

The above results suggest that the administration of zonisamide in patients with DLB is unlikely to aggravate psychiatric symptom. Since caution is advised against psychiatric symptoms such as hallucination, delusion, confusion, and delirium in the "Clinically significant adverse reactions" section of the package insert of zonisamide, it is unnecessary to provide additional caution for patients with DLB. Similar precaution as that provided for patients with PD will suffice. In administering zonisamide, attention should be paid to suicide or suicide-related behaviors. However, since caution is advised against suicide and suicide-related behaviors in the "Important Precautions," "Other adverse reactions," and "Other Precautions" sections of the package insert of zonisamide, it is unnecessary to provide additional caution for patients with DLB. Similar caution as that provided for patients with PD will suffice.

(b) Effect on cognitive function

Since decreased cognitive function is the core symptom of DLB (*Neurology.* 2017;89:1-13), an effect of zonisamide on cognitive function was evaluated using MMSE. Tables 4 and 8 show the change in MMSE total score at Week 12 from baseline in the placebo-controlled study[4)] in patients with DLB. The change (mean ± SD, number of patients) in the MMSE total score at Week 52 in the long-term treatment study[5)] was −0.6 ± 3.0 (84 patients) in the zonisamide 25 mg group and −1.0 ± 3.2 (69 patients) in the 50 mg group. In a foreign study (*J Alzheimer's Dis*. 2017;57:787-95) that followed up, for 3 years, patients with DLB treatable with antidementia drugs as was the case with the patients in the long-term treatment study on zonisamide, the MMSE total score worsened by −2.1 each year, which suggests that there is no risk of zonisamide-induced decrease in cognitive function in any of the groups.

5) After the start of zonisamide administration ("open-label period" in the placebo group and "double-blind period and open-label period" in the zonisamide group) in the phase III study

The incidence of adverse events related to dementia[6] in clinical studies in patients with DLB was, in the placebo-controlled study,[4] 0% (0 of 179) in the placebo group, 1.2% (2 of 168) (dementia with Lewy bodies and cognitive disorder in patient 1 each) in the zonisamide 25 mg group, and 1.2% (2 of 161) of patients (dementia with Lewy bodies and cognitive disorder in 1 each) in the zonisamide 50 mg group. No serious event was observed. Events leading to discontinuation of the study drug were observed in 1 patient in the zonisamide 25 mg group (dementia with Lewy bodies) and 1 patient in the zonisamide 50 mg group (cognitive disorder). In the long-term treatment study,[5] the incidence of adverse events related to dementia was 3.0% (10 of 335) (dementia with Lewy bodies in 7, dementia in 2, and cognitive disorder in 1). No serious adverse events were observed. Events leading to discontinuation of the study drug were observed in 4 patients (dementia with Lewy bodies in 3 and dementia in 1).

Thus, no significant difference was observed in the incidence of adverse events related to dementia between the placebo group and the zonisamide groups, which suggests that the administration of zonisamide to patients with DLB is unlikely to have a clinically significant effect on the cognitive function. Therefore, it is considered unnecessary to advise any particular caution regarding the aggravation of cognitive function to patients with DLB.

(c) Effect on appetite and body weight

Table 15 shows the change in body weight at Week 12 from baseline in the placebo-controlled study[4] in patients with DLB.

Table 15. Change in body weight at Week 12 from baseline in the placebo-controlled study (safety analysis population)

		No. of patients	Baseline[a]	Week 12 (LOCF)	Change[a]	Subjects with body weight decrease[b]
Phase II study	Placebo	55	54.08 ± 12.33	53.29 ± 12.18	−0.79 ± 1.72	10.9 (6)
	Zonisamide 25 mg	48	53.83 ± 10.62	52.74 ± 10.46	−1.09 ± 1.97	20.8 (10)
	Zonisamide 50 mg	49	52.48 ± 9.01	51.46 ± 9.81	−1.02 ± 2.45	26.5 (13)
Phase III study	Placebo	119	52.47 ± 9.95	52.09 ± 9.72	−0.38 ± 1.52	5.0 (6)
	Zonisamide 25 mg	117	53.58 ± 11.10	53.08 ± 11.03	−0.50 ± 1.91	11.1 (13)
	Zonisamide 50 mg	110	52.55 ± 11.07	51.64 ± 11.15	−0.91 ± 1.94	16.4 (18)

a Mean ± SD (kg)
b Percentage of subjects who showed ≥5% decrease in body weight at Week 12 (last observation carried forward [LOCF])

The incidence of appetite-related adverse events[7] in patients with DLB was, in the placebo-controlled study,[4] 1.1% (2 of 179; decreased appetite in 2) in the placebo group, 4.8% (8 of 168; decreased appetite in 5, weight decreased in 2, and decreased appetite/weight decreased in 1) in the zonisamide 25 mg group, and 9.9% (16 of 161; decreased appetite in 10, weight decreased in 5, and decreased appetite/weight decreased in 1) in the zonisamide 50 mg group. A serious event was observed in 1 patient in the zonisamide 50 mg group (decreased appetite), and events leading to discontinuation of the study drug were observed in 4 patients in the zonisamide 50 mg group (decreased appetite). In the long-term treatment study,[5] the incidence of appetite-related adverse events was 13.4% (45 of 335; decreased appetite in 19, weight decreased in 22, and decreased appetite/weight decreased in 4). A serious adverse

6) "Cognitive disorder," "Dementia," and "Dementia with Lewy bodies" in MedDRA PT
7) "Decreased appetite" and "Weight decreased" in MedDRA PT

event was observed in 1 patient (decreased appetite), and events leading to discontinuation of the study drug were observed in 4 patients (decreased appetite in 3 and weight decreased in 1).

Thus, the clinical studies suggested the risk of zonisamide inducing decreased appetite and weight decreased in patients with DLB and the dose-dependency of these risks. However, since most of the observed events were mild or moderate and caution is advised against decreased appetite and weight decreased in the "Other adverse reactions" section of the package insert of zonisamide, it is unnecessary to provide additional caution for patients with DLB. Similar caution as that provided for patients with PD will suffice.

(d) Effect of concomitant drugs

Table 16 shows the incidence of adverse events in subgroups classified by levodopa dose as well as by use/non-use of dopamine agonists, anti-dementia drugs, and Yokukansan. No significant difference was observed in the incidence of adverse events regardless of the dose of levodopa or use of anti-dementia drugs and Yokukansan. As for the concomitant use with dopamine agonists, results of the placebo-controlled study[4)] suggested that the safety of zonisamide 50 mg was inferior to that of zonisamide 25 mg, whereas in the long-term treatment study,[5)] concomitant use with dopamine agonists had no effect. The above results suggest that it is unnecessary to provide additional caution regarding concomitant drugs to patients with DLB.

Table 16. Incidence of adverse events in subgroups classified by levodopa dose or concomitant drugs (safety analysis population)

		Placebo-controlled study[a]			Long-term treatment study[b]
		Placebo	Zonisamide 25 mg	Zonisamide 50 mg	
Entire population		48.0 (86/179)	47.0 (79/168)	57.8 (93/161)	86.3 (289/335)
Levodopa dose	<300 mg	46.4 (45/97)	46.3 (44/95)	49.3 (34/69)	86.3 (158/183)
	≥300 mg	50.0 (41/82)	47.9 (35/73)	64.1 (59/92)	86.2 (131/152)
Dopamine agonists	With	35.7 (10/28)	46.2 (12/26)	85.2 (23/27)	87.2 (41/47)
	Without	50.3 (76/151)	47.2 (67/142)	52.2 (70/134)	86.1 (248/288)
Anti-dementia drugs	With	45.2 (56/124)	46.1 (59/128)	58.6 (68/116)	86.3 (207/240)
	Without	54.5 (30/55)	50.0 (20/40)	55.6 (25/45)	86.3 (82/95)
Yokukansan	With	57.1 (20/35)	38.7 (12/31)	72.4 (21/29)	82.1 (46/56)
	Without	45.8 (66/144)	48.9 (67/137)	54.5 (72/132)	87.1 (243/279)

% (number of patients with adverse events/number of patients evaluated)
a Phase II study and phase III study (double-blind period) combined; b After the start of zonisamide administration in phase III study

The above results suggest that there is no significant difference in the incidence of adverse events between patients with DLB and patients with PD, that zonisamide does not aggravate psychiatric symptoms or cognitive function, and the effect on appetite and body weight is within the tolerable range, and that the concomitant drugs had none of these effects, either. It is therefore unnecessary to advise any particular caution to patients with DLB.

PMDA's view:

In the clinical studies in patients with DLB, as were the cases with the clinical studies in patients with PD, the incidence of adverse events leading to discontinuation of the study drug tended to be higher in the zonisamide 50 mg group than in the placebo group and zonisamide 25 mg group. In patients with DLB, dose-dependent decreases in appetite and body weight were observed, and serious adverse events

and events leading to discontinuation of the study drug were observed only in the zonisamide 50 mg group. As for the effect of concomitant drugs, the incidence of adverse events in patients with DLB tended to be higher in the zonisamide 50 mg group than in the placebo group and zonisamide 25 mg group when dopamine agonists were concomitantly administered, although there are limitations to the interpretation of the data because of the small number of patients receiving some of the concomitant drugs. As for other risks, there was no significant difference between patients with DLB and patients with PD. Zonisamide had no clear effect on the psychiatric symptoms or on the cognitive function in patients with DLB. Based on the above results, there is no significant difference in the safety of zonisamide 25 mg between patients with DLB and patients with PD and zonisamide 25 mg may be used clinically in patients with DLB with the similar precaution as that provided for patients with PD. As for zonisamide 50 mg, on the other hand, since a risk exceeding that with 25 mg is suggested, the relationship between risk and benefit in adding zonisamide 50 mg to dosage regimen is discussed in Section "7.R.5 Dosage and Administration," also taking account of the relationship of efficacy between the 2 doses.

7.R.4 Indication

The applicant's explanation about the indication of zonisamide:

Clinical studies were conducted in patients who were diagnosed with "probable DLB (almost certain clinically)" according to the Clinical Diagnostic Criteria for DLB, ver. 3 (*Neurology.* 2005;65:1863-72) and had accompanying parkinsonism, and the studies confirmed the efficacy and safety of zonisamide in treating parkinsonism. Therefore, the indication for the product is proposed as "parkinsonism in dementia with Lewy bodies."

The Clinical Diagnostic Criteria for DLB, ver. 4 (*Neurology.* 2017;89:1-13) was published in 2017, and the revised criteria[8)] are expected to be used in Japan as well. Therefore, a possible effect of the revision of the diagnostic criteria on the efficacy and safety of zonisamide was investigated. Among the patients investigated in the clinical studies, 2 patients were not diagnosed as having probable DLB (almost certain clinically)[9)] according to the new diagnostic criteria (1 in the zonisamide 50 mg in phase II study, 1 in the zonisamide 25 mg group in phase III study). The efficacy and safety of zonisamide in the patient population except for the 2 subjects diagnosed as probable DLB (almost certain clinically) in both old and new diagnostic criteria were similar to those in the entire population. The efficacy and safety of zonisamide in patients[10)] who are diagnosed with probable DLB (almost certain clinically) only according to the new diagnostic criteria have not been investigated. However, since the biomarkers newly included in the new diagnostic criteria were added to improve the accuracy of the diagnosis, and the target patients for zonisamide are patients with spontaneous (uninduced) parkinsonism in DLB, the patient characteristics are unlikely to differ significantly between patients diagnosed with probable DLB (almost certain clinically) according to the old criteria and patients diagnosed according to the new

8) For the diagnosis of probable DLB (almost certain clinically), the patient must have a "core feature" (progressive deterioration in cognitive functioning) as the absolute requirement. The patient also must have (1) 2 or more of the "core features" (fluctuating cognition, recurrent visual hallucinations, spontaneous [uninduced] parkinsonism, and REM sleep behavior disorder) or (2) one of the "core features" and at least one of the "indicative biomarkers" (low dopamine transporter uptake in the basal ganglia, low uptake on ^{123}iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, and polysomnography confirmation of REM sleep without atonia).

9) Patients with a "core feature" (spontaneous [uninduced] parkinsonism) and "suggestive feature" (marked sensitivity to neuroleptics) only, according to the old diagnostic criteria

10) Patients with "indicative biomarker" (low uptake on MIBG myocardial scintigraphy or polysomnography confirmation of REM sleep without atonia) in addition to one core feature.

criteria. Therefore, the difference in the diagnostic criteria does not significantly affect the evaluation of efficacy and safety of zonisamide, and it is appropriate to use zonisamide in patients who are diagnosed with probable DLB (almost certain clinically) according to the new diagnostic criteria.

PMDA's view:
Taking account of the explanation of the applicant, the difference between the current diagnostic criteria for DLB and those used at the time when the clinical studies were conducted does not significantly affect the evaluation of the efficacy and safety of zonisamide. It is generally appropriate to indicate zonisamide for "parkinsonism in dementia with Lewy bodies." However, taking account of the facts that the clinical practice guideline for dementia recommends the use of levodopa in patients with parkinsonism in DLB, that the patients investigated in the clinical studies were patients with parkinsonism in DLB who had been taking levodopa/DCI combination drug for ≥12 weeks, together with the mechanism of action of zonisamide, it is necessary to provide caution that zonisamide should be administered to patients who are responsive and tolerant to levodopa-containing drug and in whom parkinsonism persists even after the administration of levodopa-containing drugs for a certain period. The indication and cautions to be described in the package insert will be finalized, also taking account of the comments raised in the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation about the dosage regimen of zonisamide:
By assuming from the results of the phase II study (Table 2) that zonisamide 50 mg is more effective than 25 mg for parkinsonism in DLB, the phase III study was conducted with the assumption that zonisamide 25 mg is approximately two thirds as effective as zonisamide 50 mg. As a result, a significantly better improvement was observed in the change in UPDRS Part III total score from baseline, the primary endpoint, in the zonisamide 25 mg group and 50 mg group compared with the placebo group, whereas the extent of the change was similar between the zonisamide 25 mg group and 50 mg group (Table 6). Therefore, further investigations were conducted as shown below.

(a) Dose-response relationship

In order to explore the cause for the tendency of difference in the dose response relationship between the 2 placebo-controlled studies[4)] in patients with DLB, effects of the differences in the inclusion/exclusion criteria and the patient characteristics on the efficacy were investigated. Results suggested that these differences had no significant effect on the efficacy. Then, the effect of the between-group difference in the study discontinuation rate on efficacy was investigated. In the phase III study, the percentage of patients who discontinued the study was higher in the zonisamide 50 mg group than in the 25 mg group, significantly affecting the efficacy in the 50 mg group and, as a result, the change in UPDRS Part III total score at Week 12 became similar between the 50 mg group and the 25 mg group in the phase III study. Thus, the difference in the percentage of patients who discontinued the study is a plausible cause for the observed difference in the dose response relationship of the efficacy of zonisamide between the 2 studies. If the percentage of the study discontinuation had been comparable between the studies and the treatment groups, then the efficacy of zonisamide 50 mg would have been consistently higher than that of 25 mg. However, the main reason for the study discontinuation was

adverse events in both studies, and the reason for the difference in the percentage in study discontinuation was unclear.

(b) Appropriateness of including zonisamide 50 mg in the recommended dose

In order to evaluate the appropriateness of including zonisamide 50 mg in the recommended dose in addition to zonisamide 25 mg, mainly the following investigations were carried out based on the results of the clinical studies in patients with DLB:

i) Placebo-controlled studies in patients with DLB[4)]

The dose response relationship of the efficacy tended to be different between the 2 studies, but the results of the phase III study did not differ widely from those supposed. In light of the fact that superiority of both the zonisamide 25 mg group and the 50 mg group to the placebo group was confirmed in the phase III study, both zonisamide 25 and 50 mg are considered to be effective doses against parkinsonism in DLB.

As for safety, both the incidence of adverse events and the incidence of adverse events leading to discontinuation of the study drug were higher in the zonisamide 50 mg group than in the placebo group and the zonisamide 25 mg group (Table 12), but most of the events were mild and moderate, with no significant difference in the incidence of serious adverse events or the types of adverse events observed. These results suggest that there is no significant clinical problem in treatment with zonisamide 50 mg.

ii) Phase III study in patients with DLB (open-label period)

As for efficacy, among patients who increased the dose of zonisamide from 25 mg to 50 mg at least once during the open-label period of the phase III study, patients in whom the change in the UPDRS Part III total score could be calculated (63 in the placebo group, 67 in the zonisamide 25 mg group, and 55 in the zonisamide 50 mg group [treatment groups in the double-blind period]) showed the change (mean) of −1.2, −0.9, and −2.1, respectively, in the total score after the dose increase compared with the score before the dose increase. Among patients receiving zonisamide 50 mg at Week 52, patients in whom the change in the UPDRS Part III total score could be calculated (46 patients, 51 patients, and 36 patients) showed the change of −1.76, −0.94, and −1.78, respectively, in the score at Week 52 from immediately before the dose increase. Among the patients who did not increase the dose during the open-label period, maintaining the dose of 25 mg up to Week 52 (28 patients, 24 patients, and 24 patients) and patients who increased the dose at Week 16 and maintained the dose 50 mg up to Week 52, patients in whom the change in the UPDRS Part III total score could be calculated (26 patients, 31 patients, and 21 patients) showed the change of −0.93, −3.54, −0.04, respectively, and −3.23, −1.48, −2.33, respectively, at Week 52 from Week 16. These results suggest that parkinsonism improves when the dose of zonisamide is increased from 25 mg to 50 mg.

As for safety, the types of adverse events that occurred at a high incidence during the open-label period of the phase III study were not significantly different from those observed in the double-blind period (Tables 9 and 11), and there were no severe events that occurred frequently during the long-term treatment period. The incidence of cataract tended to increase with the long-term treatment, but the

causal relationship to the study drug was ruled out in 3 of 5 patients. There were no other events that showed an increase in the incidence with long-term treatment.

Based on i) and ii) above, it is considered appropriate to include zonisamide 50 mg in the recommended clinical doses.

Taking account of (a) and (b) above and of the following, it is considered appropriate to use zonisamide 25 mg for parkinsonism in DLB as the usual dose and to allow dose adjustment within the range up to 50 mg, according to the condition of the patient:

- Symptoms of parkinsonism in DLB vary widely from patient to patient, requiring the adjustment of the dose of the therapeutic drugs depending on the condition of the patient.

- Results of a post hoc analysis suggested that zonisamide 50 mg is more effective in improving akinesia/hypokinesia[11)] than zonisamide 25 mg.

- In patients not receiving anti-PD drug other than levodopa, zonisamide 50 mg was similar in safety, but exceeded in efficacy, compared with zonisamide 25 mg.

However, in the main analysis of the phase III study, zonisamide 50 mg did not cause the improvement of motor function exceeding that achieved by zonisamide 25 mg. Therefore, it is considered necessary to provide caution that the dose of zonisamide should be adjusted to the minimum necessary dose by carefully monitoring the condition of the patient to avoid administering 50 mg without careful consideration.

PMDA's view:

As for the efficacy of zonisamide, the phase II study was positioned as an exploratory study, whereas the phase III study was positioned as a confirmatory study which was planned based on the results of the phase II study. Thus, taking account of the size and the positioning of the study, more weight should be placed on the results of the phase III study. In the phase III study, a significant improvement was observed in the zonisamide 25 mg and 50 mg groups compared with the placebo group in the change in the UPDRS Part III total score from baseline, the primary endpoint, from which it can be concluded that zonisamide 25 mg and 50 mg are effective against parkinsonism in DLB. However, it is difficult to conclude that the efficacy of zonisamide 50 mg exceeds that of 25 mg, judging from the following:

- The efficacy in each dose group should basically be evaluated based on the results of the main analysis planned in advance, instead of the results of various post hoc analyses such as the analysis of combination of specific UPDRS Part III items or the analysis of subgroups. In the primary endpoint, the efficacy in the zonisamide 50 mg group was comparable to that in the 25 mg group.

11) Among the "changes in individual UPDRS PART III scores at each evaluation time point," which are the secondary endpoints in the placebo-controlled studies in patients with DLB, a total of the scores of "finger taps," "hand movements," "rapid movements of hands," "leg agility," and "body bradykinesia and hypokinesia"

- The dose-response relationship of the efficacy tended to be different between the phase II and phase III studies for unknown reasons. However, results of the phase III study are considered to be more robust than those of the phase II study.

- The applicant presented the data of a comparison of efficacy between patients with and without dose increase in the phase III study (open-label period), but it is unclear whether the patient characteristics of each population are similar, failing to ensure the comparability, thus falling short of providing a robust evidence of a dose-response relationship.

As for safety, it cannot be concluded that the risk due to zonisamide 50 mg is similar to that due to 25 mg [see Section "7.R.3 Safety"].

Thus, since study results do not demonstrate the efficacy of zonisamide 50 mg clearly exceeding that of zonisamide 25 mg and suggest that the safety of zonisamide 50 mg is inferior to that of zonisamide 25 mg, the clinical dose in the current application should be 25 mg. Also, since the dose increase cannot be justified, the dosage regimen should be as shown below. The dosage regimen will be finalized, also taking account of comments raised in the Expert Discussion.

Dosage and administration
Zonisamide should be concomitantly administered with levodopa-containing drugs.
1. Parkinson's disease
(description omitted)
2. Parkinsonism in dementia with Lewy bodies
The usual adult dosage is 25 mg of zonisamide administered orally once daily. ~~The oral dose may be increased to 50 mg once daily according to the patient's condition.~~

(Crossed-out words are deleted from the applicant's proposal.)

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing investigations on zonisamide:
A drug use-results survey (1 year follow-up period, target sample size 500) will be conducted to investigate the safety, etc., of zonisamide in patients with parkinsonism in DLB in clinical use. In this survey, safety information will be collected with particular emphasis on hallucination, delusion, confusion, and delirium.

The target sample size of 500 was determined in order to ensure feasibility and to detect adverse drug reactions such as hallucination and visual hallucination, by taking account of the incidence of these adverse drug reactions in the specified use-results survey on patients with PD and in the clinical studies in patients with DLB.

PMDA considers that the post-marketing survey planned by the applicant is generally acceptable. Details of the post-marketing survey, etc., will be finalized, also taking account of comments raised in the Expert Discussion.

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 assessment is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that zonisamide has efficacy in the treatment of parkinsonism in patients with DLB, and that zonisamide has acceptable safety in view of its benefits. Zonisamide is clinically meaningful because it offers a new treatment option for parkinsonism in patients with DLB. Also, PMDA considers that further discussions are needed for the indication, dosage and administration, caution statements in the package insert, and post-marketing investigations.

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

Review Report (2)

May 16, 2018

Product Submitted for Approval

Brand Name	(a) Trerief Tablets 25 mg
	(b) Trerief OD Tablets 25 mg
	Trerief OD Tablets 50 mg
Non-proprietary Name	Zonisamide
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	August 30, 2017

List of Abbreviations, etc.
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 in the following. 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).

1.1 Efficacy

PMDA concluded that the results of the Japanese phase III study demonstrated the efficacy of zonisamide 25 mg and 50 mg against parkinsonism in DLB based on the primary efficacy endpoint, the change in UPDRS Part III total score. The expert advisors supported the PMDA's conclusion.

1.2 Dosage and administration

During the discussion on the dose of zonisamide provided for clinical use, the following comments were raised from the expert advisors: (1) Given the diverse symptoms of DLB, the option of zonisamide 50 mg should preferably be kept open in the clinical setting. (2) However, the most important point is that there was no difference between the zonisamide 25 mg and the 50 mg in the primary efficacy endpoint in the randomized, parallel group phase III study, and (3) many patients in the zonisamide 50 mg group discontinued the studies, and this is an unignorable result.

In light of these comments and the following observations, the conclusion was reached that the clinical dose of zonisamide for the treatment of parkinsonism in DLB should be 25 mg, and that it is difficult to approve the dose of 50 mg, judging from the results of the clinical studies.

- There is no evident effect of dose increase of zonisamide from 25 mg to 50 mg.

- The possibility cannot be excluded that zonisamide 50 mg is inferior to 25 mg in safety.
- The characteristics of patients with DLB who will benefit from zonisamide dose increase to 50 mg, if any, remain unclear.
- Zonisamide 50 mg is approved only for the improvement of wearing-off phenomenon even in patients with PD.

Accordingly, PMDA concluded that the dosage regimen of zonisamide 25-mg formulation should be defined as below. Due to the change in the dosage regimen, the applicant requested the withdrawal of the partial change application for zonisamide 50 mg on ■■, 2018.

Dosage and Administration
Zonisamide should be concomitantly administered with levodopa-containing drugs.
1. Parkinson's disease
   (description omitted)
2. Parkinsonism in dementia with Lewy bodies
   The usual adult dosage is 25 mg of zonisamide administered orally once daily.

1.3 Clinical positioning, dosage and administration

The following comments were raised from the expert advisor:
No placebo-controlled studies have been conducted to evaluate the efficacy and safety of other drugs for parkinsonism in DLB. Therefore, there is no adequate evidence for the therapeutic methods recommended by the clinical practice guideline for dementia. Given these current situations, and because of the efficacy and safety of zonisamide demonstrated in the appropriately planned clinical studies, zonisamide may serve as a new treatment option.

Also, the expert advisors supported the PMDA's conclusion that zonisamide may be recognized as a concomitant drug to be used with levodopa-containing drugs for parkinsonism in DLB for patients with persisting parkinsonism who have been treated with levodopa-containing drugs for a certain period of time.

Based on the above, PMDA concluded that the indications of zonisamide 25 mg should be defined as shown below.

Indications
1. (Description omitted)
2. Parkinsonism in dementia with Lewy bodies
   (for patients with parkinsonism persistent even after treatment with levodopa-containing drugs)

1.4 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for zonisamide should include the safety and efficacy specifications

presented in Table 17, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 18 and a general use-results survey presented in Table 19.

Table 17. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Neuroleptic malignant syndrome • Hallucination, delusion, confusion, delirium • Rhabdomyolysis • Renal and urinary calculus • Severe skin disorders (hypersensitivity syndrome, toxic epidermal necrolysis, oculomucocutaneous syndrome, erythroderma) • Blood disorders (agranulocytosis, thrombocytopenia, aplastic anaemia, aplasia pure red cell) • Interstitial pneumonia • Acute kidney injury • Hepatic dysfunction, Jaundice • Heat illness accompanying decreased sweating	Not applicable	Not applicable
Efficacy specification		
Not applicable		

Table 18. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
General use-results survey (parkinsonism in DLB)	Not applicable

Table 19. Outline of general use-results survey (draft)

Objective	To investigate the safety, etc., in clinical use
Survey method	Central registration method
Population	Patients with parkinsonism in DLB
Observation period	1 year
Planned sample size	500
Main survey items	Hallucination, delusion, confusion, delirium

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

2.1 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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (CTD 5.3.5.1.01, CTD 5.3.5.1.02) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

3. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval condition. This application is for a drug with new indications/new dosages, the re-examination period on indications and dosages and administration pertaining to this application is 4 years.

Indications

1. Parkinson's disease
   (for patients who did not respond adequately to a combination of levodopa-containing drugs and other antiparkinsonian drugs)
2. Parkinsonism in dementia with Lewy bodies
   (for patients with parkinsonism persistent even after treatment with levodopa-containing drugs)

(Underline denotes addition.)

Dosage and administration

Zonisamide should be concomitantly administered with levodopa-containing drugs.

1. Parkinson's disease
   The usual adult dosage is 25 mg of zonisamide administered orally once daily. For the improvement of the diurnal variation in the symptoms of Parkinson's disease (wearing-off phenomenon), 50 mg of zonisamide is administered orally once daily.
2. Parkinsonism in dementia with Lewy bodies
   The usual adult dosage is 25 mg of zonisamide administered orally once daily.

(Underline denotes addition.)

Approval Condition

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

Appendix

List of Abbreviations

BPSD	Behavioral and Psychological Symptoms of Dementia
CI	Confidence interval
Clinical practice guideline for dementia	Clinical practice guideline for dementia (2017), first edition, Igaku Shoin; 2017
DCI	Dopa decarboxylase inhibitor
DLB	Dementia with Lewy bodies
HPLC	High performance liquid chromatography
IC_{50}	50% inhibitory concentration
Levodopa/DCI combination drug	Combination drug containing levodopa and a peripheral DOPA decarboxylase inhibitor
LOCF	Last observation carried forward
LSD	Least significant difference
LT	Long-term population
MAO	Monoamine oxidase
MAO-B	Monoamine oxidase-B
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	^{123}Iodine-metaiodobenzylguanidine
mITT	Modified intention-to-treat
MMRM	Mixed model for repeated measures
MMSE	Mini-mental state examination
NPI	Neuropsychiatric inventory
PD	Parkinson's disease
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
SOC	System Organ Class
Trerief	Trerief Tablets, Trerief OD Tablets
UPDRS	Unified Parkinson’s disease rating scale