

## Report on the Deliberation Results

December 4, 2008

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

<b>Brand Name</b>	Trerief Tablets 25 mg
<b>Non-proprietary Name</b>	Zonisamide (JAN*)
<b>Applicant</b>	Dainippon Sumitomo Pharma Co., Ltd.
<b>Date of Application</b>	September 28, 2005

### Results of Deliberation

In its meeting held on November 28, 2008, the First Committee on New Drugs concluded that 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 product is not classified as a biological product or a specified biological product, the re-examination period is 4 years, and the drug product and its drug substance are both classified as powerful drugs.

*\*Japanese Accepted Name (modified INN)*

*This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.*

## Review Report

November 12, 2008

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).

<b>Brand Name</b>	Trerief Tablets 25 mg (changed from Tremode Tablets 25 mg [proposed name])
<b>Non-proprietary Name</b>	Zonisamide
<b>Applicant</b>	Dainippon Pharmaceutical Co., Ltd. (currently Dainippon Sumitomo Pharma Co., Ltd.)
<b>Date of Application</b>	September 28, 2005 (marketing application for a drug)
<b>Dosage Form/Strength</b>	Film-coated tablets, each containing 25 mg of Zonisamide
<b>Application Classification</b>	Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage
<b>Items Warranting Special Mention</b>	None
<b>Reviewing Office</b>	Office of New Drug II

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## Review Results

November 12, 2008

<b>Brand Name</b>	Trerief Tablets 25 mg (changed from Tremode Tablets 25 mg [proposed name])
<b>Non-proprietary Name</b>	Zonisamide
<b>Applicant</b>	Dainippon Pharmaceutical Co., Ltd. (currently Dainippon Sumitomo Pharma Co., Ltd.)
<b>Date of Application</b>	September 28, 2005 (marketing application for the drug)

### Results of Review

On the basis of the data submitted, PMDA has concluded that Trerief Tablets 25 mg (hereinafter referred to as the product) has efficacy and the safety in the treatment of patients with Parkinson's disease who had inadequate response to a combination of levodopa-containing drugs with other antiparkinsonian drugs.

The efficacy of the product was investigated in a phase III study involving patients with Parkinson's disease who had inadequate response to a combination of levodopa-containing drugs with other antiparkinsonian drugs, based on the information gained during the product development. Results confirmed the superiority of the zonisamide 25 mg to placebo in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III total score, the primary endpoint. PMDA considers that the results demonstrated the efficacy of the product.

Safety analyses in the phase III study revealed no major differences in the adverse events identified and their incidences between the product and placebo. PMDA considers that there are no major problems in the use of the product to treat patients with Parkinson's disease.

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

### Indication

Parkinson's disease (for patients who did not respond adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)

### Dosage and Administration

Zonisamide should be concomitantly administered with levodopa-containing drugs.  
The usual adult dosage is 25 mg of zonisamide administered orally once daily.

## Review Report (1)

September 8, 2008

### I. Product Submitted for Approval

<b>Brand Name</b>	Trerief Tablets 25 mg (changed from Tremode Tablets 25 mg [proposed name])
<b>Non-proprietary Name</b>	Zonisamide
<b>Applicant</b>	Dainippon Pharmaceutical Co., Ltd. (currently Dainippon Sumitomo Pharma Co., Ltd.)
<b>Date of Application</b>	September 28, 2005
<b>Dosage form/Strength</b>	Film-coated tablets, each containing 25 mg of Zonisamide
<b>Proposed Indication</b>	Parkinson's disease (for patients who have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)

### Proposed Dosage and Administration

The usual adult dosage is 25 to 50 mg of zonisamide administered orally once daily.

### II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The following is an outline of the data submitted by the applicant at the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA).

#### 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 on March 31, 1989 as an antiepileptic drug (brand names Excegran Tablets 100 mg and Excegran Powder [changed to Excegran Powder 20% on January 19, 2004]). Zonisamide was also approved as an antiepileptic drug in the US in March 2000 and is approved in 36 foreign countries as of May 2008.

When zonisamide was administered to Japanese patients with Parkinson's disease with the purpose of treating intercurrent convulsive seizures, the treatment not only caused the seizures to disappear, but also improved the symptoms of Parkinson's disease. Therefore, zonisamide was developed as an antiparkinsonian drug from 2001 and, recently, a marketing application has been submitted by the applicant, with the proposed indication of "Parkinson's disease (for patients who have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)," based on the results of Japanese clinical studies, etc.

At the [REDACTED] consultation on [REDACTED], 20[REDACTED] before this application, PMDA recommended the applicant to conduct an additional clinical study for the following reasons: (1) Patients enrolled in clinical studies were not homogeneous, precluding the identification of the patient population indicated for zonisamide, (2) given the results of the clinical and nonclinical studies obtained, it appears difficult to determine the clinical positioning of zonisamide and to interpret the results of the clinical studies, (3) it is necessary to investigate the most appropriate parameter for assessing the efficacy of zonisamide, and (4) it is difficult to conclude that the recommended clinical dose of zonisamide has been established. However, [REDACTED] the applicant submitted the application without conducting a new clinical study. Afterwards, the applicant conducted an additional clinical study from [REDACTED] 20[REDACTED] in order to resolve problems pointed out at [REDACTED] consultation during the review process, and submitted the results of the study.

## **2. Physicochemical properties and specifications**

### **2.A Summary of the submitted data**

Zonisamide (molecular formula  $C_8H_8N_2O_3S$ , molecular weight 212.23) is a compound listed in the Japanese Pharmaceutical Codex (JPC) and is the same as the active ingredient of approved drugs Excegran Tablets 100 mg and Excegran Powder 20%.

#### **2.A.(1) Drug substance**

No new data were submitted.

#### **2.A.(2) Drug product**

##### **2.A.(2).1 Description and composition of the drug product**

Zonisamide 25 mg drug product (Trierief Tablets 25 mg, hereinafter referred to as the product) is pale yellow, film-coated tablets composed of (1) [REDACTED] comprising the drug substance, [REDACTED] (lactose hydrate and microcrystalline cellulose), [REDACTED] (low substituted hydroxypropylcellulose), [REDACTED] (hydroxypropylcellulose), and [REDACTED] (magnesium stearate and light anhydrous silicic acid) and (2) [REDACTED] comprising [REDACTED] (hypromellose, macrogol 6000, titanium oxide, talc, and light anhydrous silicic acid) and [REDACTED] (yellow ferric oxide).

##### **2.A.(2).2 Formulation development**

The drug product is [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. [REDACTED] of the product has been changed from that of Excegran Tablets 100 mg. Also, yellow ferric oxide is added as [REDACTED] in order to differentiate the product from white Excegran Tablets 100 mg. The biological equivalence (BE) between Excegran Tablets 100 mg and the product has been confirmed [see Section 4.(i).A.(1)].

##### **2.A.(2).3 Manufacturing process**

The product is manufactured through the following 7 processes:

[REDACTED] process: [REDACTED].

process: .  
process: .  
process: .  
process: .  
process: .  
process: .  
to prepare film-coated tablets.

Packaging and labeling process: The tablets are filled in a polyvinylchloride-polyvinylidene chloride-polyethylene laminated sheet using a press through packaging (PTP) machine, which is then heat-sealed with aluminum foil, cut into PTP sheets, and packaged in paper boxes.

Among the above processes, , , and processes are identified as the critical steps, and in-process control parameters and action limits have been established for the critical steps.

#### **2.A.(2).4 Control of drug product**

The proposed specifications for the drug product include description (visual inspection), identification (ultraviolet-visible spectrophotometry [UV]), uniformity of dosage unit (content uniformity [UV]), dissolution (dissolution test [UV]), and content (UV).

#### **2.A.(2).5 Stability of drug product**

In support of the present application, results of an accelerated testing (40°C/75% RH, 6 months) of 3 batches (preceding batches) each of the product stored in polyvinyl chloride/aluminum foil PTP package (usual PTP package) and in polyethylene bottles (bottle packages) were submitted as data of the stability study. Since it was determined during the review process that the 6-month data of the accelerated testing were insufficient for assessing the stability of the product, data of a long-term testing (25°C/60% RH, months) stored in usual PTP packages were submitted as additional data.

Description, identification (UV), dissolution (UV), content (UV and high-performance liquid chromatography [HPLC]), related substances (HPLC), water content, and hardness were measured at the start and after storage for and 6 months in the accelerated testing and at the start and after storage for 3, 6, 9, 12, 18, 24, 36, , , and months in the long-term testing. In the accelerated testing, decreased hardness was observed in the usual PTP package but the dissolution rate was within the specification, and no significant changes were observed in other parameters. No significant changes were observed in any of the parameters in the bottle packages. In the long-term testing, the dissolution rate was below the specification at the application (proposed specification, in minutes, in minutes) in some of the batches after storage for months, but an additional test confirmed the conformity to the proposed specification. No significant changes were observed for other parameters.

However, in the stability study of batches manufactured after the application (additional batches), a tendency of delayed dissolution possibly due to moisture absorption during storage was observed. Therefore, an accelerated testing (40°C/75% RH, 6 months) was conducted on the additional batches (3 batches each) stored in a polyvinylchloride-polyvinylidene chloride-polyethylene laminated sheet/aluminum foil PTP package (highly moisture-proof PTP package) as well as in a usual PTP package according to the proposed specifications and the control specifications for the study drug (study drug specifications, [REDACTED] in [REDACTED] minutes, [REDACTED] in [REDACTED] minutes). In the usual PTP packages, a tendency of decrease in the hardness and decreased dissolution rate were observed, and deviations from the proposed specification and the study drug specification were observed in 1 batch. In the highly moisture-proof PTP packages, a tendency of decreases in the hardness and dissolution rate was observed and deviation of the mean dissolution rate from the proposed specification was observed with 1 batch, while all batches conformed to the study drug specifications. No changes over time were observed in any other parameter with either packaging.

As a result of the above study, application for the bottle package was withdrawn because of concern of moisture absorption due to repeated opening and closing of the cap over a long-term period during the use in clinical settings. Also, the usual PTP package was replaced by the highly moisture-proof PTP package. Since some batches did not meet the proposed specifications even under storage in highly moisture-proof PTP package, the specification for dissolution test was changed from “[REDACTED] in [REDACTED] minutes, [REDACTED] in [REDACTED] minutes (proposed specification)” to “[REDACTED] in [REDACTED] minutes, [REDACTED] in [REDACTED] minutes (study drug specification),” and the data of the long-term testing on the additional batches under storage in the usual PTP package and in the highly moisture-proof PTP package were submitted.

The long-term testing (25°C/60% RH) of the additional batches was completed up to 12 months, and in the usual PTP package, some of individual dissolution rate in 1 batch was below the study drug specification but the dissolution rate was within the specification for the remaining 2 batches. In the highly moisture-proof PTP package, some of individual dissolution rate in 1 batch was below the study drug specification but the dissolution rate was within the specification for the other 2 batches. An additional test was conducted on the batch that had shown the dissolution rate below the study drug specification, and the results confirmed conformance to the specification. No significant changes were observed for the parameters other than the dissolution rate for any of the batches tested.

Based on the above results, it is considered that the drug product is stable over a long-term period when stored in the highly moisture-proof PTP package. The long-term testing will be carried out continuously for [REDACTED] months with the preceding batches and for 36 months with the additional batches.

### **2.A.(3) Reference standards or materials**

“Zonisamide Reference Standard” (JPC) was used.

## **2.B Outline of the review by PMDA**

### **2.B.(1) Control of residual solvents in the drug substance**

Since the drug substance is identical with that of Excegran Tablets 100 mg and Excegran Powder 20%, no new data were submitted in the present application. However, since the manufacture of the drug

substance includes a process that uses [REDACTED], which is classified as a Class 1 solvent in pharmaceutical product (solvent that should be avoided) by the “Guideline for Residual Solvents” (PMSB/ELD Notification No. 307 Appendix dated March 30, 1998), PMDA instructed the applicant to develop a manufacturing process that does not use [REDACTED] and, if the use of [REDACTED] cannot be avoided, to strictly control the residual level by establishing appropriate control standards.

The applicant’s response:

Because [REDACTED] is classified as a Class 1 solvent, extensive studies have been carried out on possible alternative solvents. However, none of the solvents tested allowed the manufacture of the finished drug substance of the same quality as that of the drug substance manufactured using [REDACTED], resulting in an increased level of residual by-products, poor quality in appearance, etc. For this reason, [REDACTED] has been used out of necessity. The residual level of [REDACTED] in drug substance is well controllable below the allowable limit ([REDACTED] ppm) specified by the “Guidelines for Residual Solvents” by the procedure to reduce [REDACTED] in the final purification process. However, taking account of the fact that [REDACTED] is a solvent to be avoided, the residual level of [REDACTED] will be added as a process control parameter in the final purification process in order to control the residual level constantly below the allowable limit. The data of the residual level of [REDACTED] will be checked at the receipt of the drug substance together with the results of the tests for the specification items.

PMDA’s view:

Since [REDACTED] is classified as a Class 1 solvent by the “Guidelines for Residual Solvents” because of the toxicity concern, it is necessary to investigate and develop a manufacturing process that does not use said solvent. However, the control method and the control standards proposed by the applicant are acceptable.

## **2.B.(2) Appropriateness of changing the specifications for the dissolution of the drug product from the proposed specification to the study drug specification**

PMDA asked the applicant to explain the appropriateness of changing the specification of the dissolution test from the proposed specification “dissolution rate of [REDACTED] in [REDACTED] minutes and [REDACTED] in [REDACTED] minutes” to the study drug specification “dissolution rate of [REDACTED] in [REDACTED] minutes and [REDACTED] in [REDACTED] minutes,” together with the reason for the difference in the dissolution rate between the preceding batches and the additional batches.

The applicant’s response:

It is considered that the following factors contributed to the observed difference in the dissolution rate in [REDACTED] minutes between the preceding batches and the additional batches. Thus, the drug product is designed to suppress the initial release of the drug substance, and the specification for the dissolution test requires measurement of the dissolution rate at 2 time points. The dissolution rate in [REDACTED] minutes differed between the preceding batches and the additional batches presumably because of the difference in the extent of the initial release. As for the possible cause during the manufacture, although each batch is manufactured by the same manufacturing process, it is likely that there were differences in



between the preceding batches and the additional batches which was caused by the differences in [REDACTED] and in [REDACTED] in each process ([REDACTED]). However, it is practically impossible to identify the root cause. Further investigations will be continued to identify main factors causing the variations of the dissolution rate. Currently, the possibility cannot be excluded that future batches may show variations in the dissolution rate as observed in the additional batches. For reasons stated above, the specification for the dissolution test was changed from that proposed to that for the study drug, based on the data of the test on the additional batches. The drug product should be controlled appropriately by the dissolution specification determined by taking account of the variations among individual tablets or batches instead of those determined based on the mean and variation as is the case with the content specifications. Therefore, the dissolution rate in [REDACTED] minutes was selected at [REDACTED] taking account of the dissolution specification ([REDACTED] in [REDACTED] minutes) adopted in the control of the study drug. Thus, the proposed specification which had been developed to more strictly control the drug product after marketing is reversed to the study drug specification that had been adopted to control the batches of the study drug used in clinical studies. It is therefore expected that the drug product has the same efficacy and the safety as those of the formulation used in clinical studies.

PMDA asked the applicant to explain the appropriateness of controlling the product using the dissolution specification applied to the study drug, taking account of the effect of the dissolution behavior on the pharmacokinetics, efficacy, and safety of zonisamide.

The applicant's response:

A preliminary membrane permeability test conducted using Caco-2 cells demonstrated a favorable membrane permeability of zonisamide, suggesting that dissolution within the digestive tract is the rate-limiting step of the absorption of zonisamide after administration. In light of the observations that the mean elimination half-life ( $T_{1/2}$ ) of zonisamide was approximately 80 hours and the mean time to the maximum concentration ( $T_{max}$ ) was approximately 3 hours, the difference in the dissolution rate during the early stage after administration (within [REDACTED] minutes) is unlikely to have any significant effect on the pharmacokinetics of zonisamide, as suggested by the following findings:

- 1) In a dissolution test of Excegran Tablets 100 mg and Trerief (25 mg) conducted for the present application, Trerief showed a higher dissolution rate of [REDACTED]% to [REDACTED]% in [REDACTED] to [REDACTED] minutes. However, both products met the criteria for BE regarding the maximum plasma concentration ( $C_{max}$ ) and the area under the plasma concentration-time curve from administration until the time of the final measurable concentration ( $AUC_{0-t}$ ) [see Section 4.(i).A.(1)].
- 2) In a dissolution test conducted for the reevaluation of Excegran Tablets 100 mg and Excegran Powder 20%, Excegran Powder showed a [REDACTED]% higher dissolution rate in [REDACTED] minutes and Excegran Tablets showed a [REDACTED]% to [REDACTED]% higher rate in [REDACTED] to [REDACTED] minutes, while pharmacokinetic parameters after oral administration were similar between the two products (Data F-12 submitted for the previous approval).
- 3) The data observed after administration of 4 tablets of Trerief (25 mg) in the BE study (2) conducted for the present application were fitted to a 1-compartment model with absorption process, and plasma concentration was simulated using a pharmacokinetics/pharmacodynamics

(PK/PD) analysis software WinNonlin. The simulated plasma concentration was compared with that obtained by decreasing the absorption rate constant from the simulated constant by 75% or 50%. As a result, the applicant determined that decrease in the absorption rate constant, i.e., decrease in the dissolution rate, minimally affects the plasma concentration under steady state.

In pharmacokinetic terms, the above results suggest that the difference in the dissolution rate within ■ minutes have only an insignificant effect on the efficacy and safety of zonisamide. Also, in light of the observation that, in the stability study of the additional batches, the batches with a low dissolution rate in ■ minutes (dissolution rate ■ ± ■% [mean ± standard deviation (SD)]) showed a dissolution rate of ■% to ■% in ■ minutes, indicating an almost complete dissolution. These results suggest that the product that meets the dissolution specification (dissolution rate ■ in ■ minutes) is expected to have the same efficacy and safety as those observed in the clinical studies, without significantly changing the pharmacokinetics.

PMDA considers that the differences in the dissolution behavior between the proposed specification and the specifications used in the clinical studies minimally affect the efficacy and safety of zonisamide if at all and that it is appropriate to change the dissolution specification of the product to that for the study drug. The specification will be finalized, taking account of comments raised in the Expert Discussion.

### **2.B.(3) Establishment of shelf life for the product**

PMDA asked the applicant to determine the shelf life of the product from the results so far obtained from the stability studies (additional batches, long-term testing for 12 months and accelerated testing for 6 months) and explain the appropriateness of the shelf life based on the scientific evidence.

The applicant's response:

With the highly moisture-proof PTP packages of the additional batches, the mean dissolution rate in ■ minutes was predicted for the batches after ■ months of the long-term testing, based on the mean dissolution rate in ■ minutes (the study drug specification) determined based on the data obtained up to 12 months of the long-term testing so far completed. Usually, chemical reactions such as decrease in content and formation of degradation products are estimated by reaction kinetics, whereas since no general method has been established for the estimation of attributes of drug product such as dissolution behavior, it was assumed that the storage period and the mean dissolution rate ■.

Estimation on each batch for ■ showed that the lower limit of the 95% confidence interval of the predicted mean dissolution rate in ■ minutes in 2 batches of the long-term testing after ■ months was ■% and ■%, respectively, suggesting a conformity with the study drug specification. However, the dissolution rate was ■% for 1 batch, predicting the nonconformity with the specification. It was predicted that the longest period that meets the dissolution rate of ■% in ■ minutes is ■ months.

For ■, as is the case with ■, the lower limit of the 95% confidence interval of the predicted mean dissolution rate in ■ minutes in 2 batches of the long-term testing after ■

months was ■■■% and ■■■%, respectively, suggesting a conformity with the study drug specification, whereas the dissolution rate was ■■■% for 1 batch, predicting the nonconformity with the specifications. It was predicted that the longest period that meets the dissolution rate of ■■■% in ■■■ minutes is ■■■ months.

Based on the above results, the applicant considers that the shelf life of the product stored in highly moisture-proof PTP packages should be 24 months by adding 12 months to 12 months, the period with observed data available according to the concept of the “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003).

PMDA considers that the response of the applicant is acceptable. However, since the shelf life is also related to the dissolution specification of the drug product, the decision will be finalized, taking account of comments raised in the Expert Discussion.

### **3. Non-clinical data**

#### **3.(i) Summary of pharmacology studies**

##### **3.(i).A Summary of the submitted data**

##### **3.(i).A.(1) Primary pharmacodynamics**

##### **3.(i).A.(1).1 Antiparkinsonian effect in combination with L-3,4-dihydroxyphenylalanine (L-DOPA) (*in vivo*)**

##### **(a) Effect on L-DOPA-induced hyperkinesia in a rat model of Parkinson’s disease induced by reserpine (Data 4.2.1.1-1)**

Male Std:Wistar rats (n = 7-8) were subcutaneously administered reserpine 5 mg/kg 23 to 25 hours before the behavioral test to induce parkinsonian symptoms (reserpine-treated rats). L-DOPA (containing 1/4 amount of benserazide hydrochloride on a salt weight basis, the same below) was orally administered to reserpine-treated rats at 200 mg/kg, and the locomotor activity of each rat was measured every 15 minutes for 210 minutes after L-DOPA administration. Zonisamide (5, 15, or 50 mg/kg) or the vehicle was administered orally approximately 90 minutes before the start of locomotor activity measurement, and selegiline hydrochloride (selegiline; 3.3, 5, or 7.5 mg/kg), bromocriptine mesilate (bromocriptine; 1, 3, or 10 mg/kg), amantadine hydrochloride (amantadine; 2.5, 5, or 10 mg/kg), or the respective vehicle was administered intraperitoneally immediately before the start of locomotor activity measurement.

In order to increase the sensitivity of detecting the effect of each test drug, the locomotor activity during 90 to 210 minutes after the start of locomotor activity measurement was used as the primary endpoint, and the total locomotor activity during the period from 0 to 210 minutes as the secondary endpoint, based on the results of a preliminary test. Animals in the zonisamide group, selegiline group, and bromocriptine group showed a dose-dependent increase in the locomotor activity during 90 to 210 minutes, with a statistically significant increase observed at  $\geq 15$  mg/kg,  $\geq 5$  mg/kg, and  $\geq 10$  mg/kg, respectively (comparison with the respective vehicle group). Animals in the amantadine group showed no significant increase at any dose. As for total locomotor activity, animals in the zonisamide group and the selegiline group showed a dose-dependent increase, with a statistically significant increase at  $\geq 15$  mg/kg and  $\geq 5$  mg/kg, respectively, whereas animals in the bromocriptine group and the amantadine

group showed no significant increase. Zonisamide 15 mg/kg and selegiline 5 mg/kg showed similar results of the time-course patterns of L-DOPA-induced hyperkinesia. Both drugs did not show a major difference in the peak locomotor activity compared with the vehicle group, but showed continuous increase in locomotor activity after the occurrence of peak. Also, the zonisamide 50 mg/kg group, the bromocriptine  $\geq 3$  mg/kg groups, and the amantadine 10 mg/kg group showed a delay of 15 to 30 minutes in the occurrence of peak compared with the vehicle group.

The above results suggested that zonisamide has a dose-dependent enhancing effect on L-DOPA-induced hyperkinesia although zonisamide partly responses in a different way from the existing antiparkinsonian drugs.

**(b) Effect on L-DOPA-induced rotational behavior in a rat model of Parkinson's disease prepared by 6-hydroxydopamine-induced neuronal destruction of unilateral nigrostriatal dopaminergic neuron (Data 4.2.1.1-2 and 4.2.1.1-3)**

Male Std:Wistar rats were injected with 6-hydroxydopamine (6-OHDA) hydrochloride (9  $\mu$ g/4  $\mu$ L/site) into the unilateral median forebrain bundle, and were subcutaneously administered apomorphine hydrochloride (apomorphine, 0.05 mg/kg) 4 weeks later. Rats that rotated  $\geq 150$  times toward the nondestructive side for 1 hour (unilaterally 6-OHDA-treated rats) were subjected to the following tests:

i) Prolongation of the duration of L-DOPA effect

The unilaterally 6-OHDA-treated rats (n = 7-8) were intraperitoneally administered L-DOPA 5 mg/kg, and the duration of rotation toward the nondestructive site (the time from the start of the rotational behavior until the behavior immediately before the time showing no further rotation toward the nondestructive side for  $\geq 5$  minutes) was measured. The total number of rotations and the number of rotations per 10 minutes were measured as secondary endpoints. Zonisamide (10, 30, or 100 mg/kg) or the vehicle was administered orally at 2 hours before dosing of L-DOPA, and selegiline (1.0, 5.0, or 20 mg/kg) or the vehicle was administered intraperitoneally at 1 hour before dosing of L-DOPA.

Zonisamide 100 mg/kg and selegiline 20 mg/kg significantly increased the duration of L-DOPA-induced rotational behavior as compared to the respective vehicles. In contrast, zonisamide did not have influence on the total number of L-DOPA-induced rotations although zonisamide tended to decrease the number of rotations per 10 minutes up to 45 minutes after dosing of L-DOPA. The selegiline 20 mg/kg group showed an increase in the total number of rotations accompanied by a continuous increase in the number of rotations per 10 minutes.

The above results suggested that a single-dose of zonisamide has an effect that prolongs L-DOPA-induced rotational behavior although it partly acts in a different way from selegiline.

ii) Improvement of decrease in the duration of rotational behavior caused by repeated administration of high dose of L-DOPA methyl ester hydrochloride (methyl L-DOPA)

The unilaterally 6-OHDA-treated rats were subcutaneously administered apomorphine 0.05 mg/kg at intervals of 2 to 4 days for a total of 12 to 13 doses. Rats showing stabilized rotational behavior received intraperitoneally a challenge dose (dose for evaluating the duration of the rotational behavior) of methyl L-DOPA 25 mg/kg (since L-DOPA is insoluble in water at high concentrations, methyl L-DOPA which

is easily converted to L-DOPA by hydrolase in blood was used instead), and the duration of rotation toward the nondestructive side (duration of rotational behavior following the initial administration) was measured. Then, these rats were intraperitoneally administered high-dose methyl L-DOPA (50 mg/kg) twice daily (once daily on Saturdays and Sundays) for 15 or 16 days to induce wearing-off-like phenomenon. After the repeated administration, these rats were intraperitoneally administered again a challenge dose of methyl L-DOPA 25 mg/kg. Rats (n = 5-7) showing a decrease to  $\leq 85\%$  in the ratio of the duration of rotational behavior relative to the duration following the initial administration (decrement ratio) were treated with zonisamide 25, 50, or 100 mg/kg, selegiline 5 mg/kg, amantadine 50 mg/kg, or vehicle orally once daily for 14 days. At 1 hour after dosing of the test drug on Day 1, 7, and 14, the duration of rotational behavior was measured after a single intraperitoneal dose of methyl L-DOPA (25 mg/kg). In order to maintain the wearing-off-like phenomenon induced by administration of methyl L-DOPA 25 mg/kg, once daily administration of methyl L-DOPA 50 mg/kg was continued until Day 13 of the test drug administration. On Day 14 of the repeated administration, Zonisamide 50 and 100 mg/kg and selegiline significantly increased the decrement ratio of the duration of rotational behavior as compared with the vehicle, whereas amantadine did not show such increase.

These results suggested that repeated administration of zonisamide improves the wearing-off-like phenomenon.

**(c) Influence on L-DOPA effect in Parkinson's disease model monkeys prepared by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopamine neuron destruction (Data 4.2.1.1-4 and 4.2.1.1-5)**

Male cynomolgus monkeys were administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 0.6 mg/kg by continuous infusion (flow rate 2 mL/min for 20 minutes) into the unilateral common carotid artery twice at 1-week interval, followed by the subcutaneous administration of apomorphine 0.6 mg/kg every other day for a total of 3 doses. Animals showing rotational behavior toward the nondestructive side (unilaterally MPTP-treated monkeys) were subjected to the following tests. As the dose of methyl L-DOPA inducing rotational behavior (challenge dose), the dose that induced the rotational behavior for  $\geq 10$  minutes in the preliminary test and showed an increase in the duration of the rotational behavior even at twice or higher doses was used.

**i) Single-dose administration**

Zonisamide (12.5, 25, or 50 mg/kg) or vehicle was administered orally to the same unilaterally MPTP-treated monkeys (n = 8) by the cross-over method. After 2 hours, a challenge dose of methyl L-DOPA (7.5-15 mg/kg) was administered intramuscularly, and the duration of the rotational behavior (time from the start of the rotational behavior until the time when rotation toward the nondestructive side was not observed for  $\geq 10$  minutes or until immediately before the time when the animal showed a 360° rotation toward the destructive side) was measured. Also, as secondary endpoints, the total number of rotations toward the nondestructive side, unilateral parkinsonian symptom score at the peak rotational behavior, and plasma zonisamide concentration were measured. In the zonisamide 12.5 and 25 mg/kg groups, the duration of L-DOPA-induced rotational behavior and the total number of rotations tended to increase compared with the vehicle group. However, the increases were less prominent in the 25 mg/kg group compared with the 12.5 mg group, and the parameter values were lower in the 50 mg/kg group compared

with the vehicle group. Unilateral parkinsonian symptom score did not show marked change at any dose tested. Plasma zonisamide concentration increased with dose.

ii) Repeated-dose administration

Zonisamide (1, 3, or 10 mg/kg) or vehicle was administered orally for a total of 14 doses (5 days) at intervals of approximately 8 hours by the cross-over method to the same unilaterally MPTP-treated monkeys (n = 8) that had completed the above single-dose administration study. At 2 hours after the final dose, a challenge dose of L-DOPA methyl ester (7.5-20 mg/kg) was administered intramuscularly, and the animals were subjected to evaluation of rotational behaviors and other parameters in the same manner as in the single-dose administration. In the zonisamide groups, duration of L-DOPA-induced rotational behavior and the total number of rotations tended to increase with dose. No marked changes were observed in unilateral parkinsonian symptom score at any dose. Plasma zonisamide concentration increased with dose.

Results of i) and ii) above suggested that both single- and repeated-dose administration of zonisamide to Parkinson's disease-model monkeys enhances and prolongs L-DOPA-induced hyperkinesia, and that, in repeated administrations, zonisamide is also effective at doses that cause a higher plasma concentration than that achieved by single-dose administration.

**3.(i).A.(2).2) Mechanism of action (*in vitro*, *in vivo*)**

**(a) *In vitro* inhibition of monoamine oxidase MAO activity (Data 4.2.1.1-6 and 4.2.1.1-7)**

Mitochondrial/synaptosomal membrane fractions were prepared from striatal tissue of male Std:Wistar rats, and monoamine oxidase (MAO) activity of type A (MAO-A) and type B (MAO-B) were measured using [ $^{14}$ C]-5-hydroxytryptamine (5-HT), [ $^{14}$ C]- $\beta$ -phenylethylamine ( $\beta$ -PEA), and [ $^{14}$ C]-dopamine as substrates (which undergo oxidative deamination reaction catalyzed by MAO-A, MAO-B, and both MAO-A and MAO-B, respectively), and the inhibitory effect of zonisamide, clorgyline hydrochloride (clorgyline; irreversible MAO-A inhibitor), and selegiline (irreversible MAO-B inhibitor) was investigated. The 50% inhibitory concentration (IC<sub>50</sub>) of zonisamide against each activity was 280, 28, and 96  $\mu$ mol/L, respectively, when [ $^{14}$ C]-5-HT, [ $^{14}$ C]- $\beta$ -PEA, and [ $^{14}$ C]-dopamine were substrates. IC<sub>50</sub> of clorgyline was 0.013 and 0.011  $\mu$ mol/L, respectively, when [ $^{14}$ C]-5-HT and [ $^{14}$ C]-dopamine were substrates. IC<sub>50</sub> of selegiline hydrochloride was 0.051 and 6.2  $\mu$ mol/L, respectively, when [ $^{14}$ C]- $\beta$ -PEA and [ $^{14}$ C]-dopamine were substrates.

Each test drug was preincubated (37°C for 30 minutes) with the membrane fraction to conduct a similar investigation. IC<sub>50</sub> of clorgyline and selegiline, irreversible inhibitors of MAO, decreased as compared with the IC<sub>50</sub> observed without preincubation. In contrast, IC<sub>50</sub> of zonisamide had no effect by the preincubation.

In a similar study using mitochondrial/synaptosomal membrane fraction prepared from the striatum of male cynomolgus monkeys, IC<sub>50</sub> of zonisamide was 520, 58, and 10  $\mu$ mol/L, respectively, when [ $^{14}$ C]-5-HT, [ $^{14}$ C]- $\beta$ -PEA, and [ $^{14}$ C]-dopamine were substrates. IC<sub>50</sub> of clorgyline was 0.013 and 0.86  $\mu$ mol/L when [ $^{14}$ C]-5-HT and [ $^{14}$ C]-dopamine were substrates. IC<sub>50</sub> of selegiline was 0.0023 and 0.0075  $\mu$ mol/L when [ $^{14}$ C]- $\beta$ -PEA and [ $^{14}$ C]-dopamine were substrates.

The above results suggested that zonisamide inhibits MAO with relatively higher selectivity for MAO-B.

**(b) Affinity for receptors and transporters (Data 4.2.1.1-8)**

Inhibitory activity of zonisamide against various receptors (including those for dopamine, acetylcholine, glutamic acid, adrenaline, adenosine,  $\gamma$ -aminobutyric acid [GABA]/benzodiazepine, cannabinoid, cholecystokinin [CCK], melanocortin, opiate, and somatostatin) and transporters (including those for monoamine, dopamine, serotonin, norepinephrine, GABA, and adenosine) was investigated. Zonisamide (300  $\mu$ mol/L) inhibited the binding of representative radioactive ligands to respective receptors and transporters by 21.14% at the maximum.

The above results suggested that zonisamide has no or extremely low affinity for these receptors and transporters.

**(c) *In vivo* effect on dopamine turnover in striatal tissue (Data 4.2.1.1-9 and 4.2.1.1-10)**

Zonisamide (10, 30, or 100 mg/kg) or vehicle was administered orally to male Std:Wistar rats (n = 8) and, after 3 hours, contents of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the striatal tissue were measured. Zonisamide showed little change in dopamine content in the striatum at any dose compared with the vehicle group, whereas dopamine turnover rate ([DOPAC + HVA]/dopamine in molar ratio) decreased in a dose-dependent manner, showing a significant decrease at 30 and 100 mg/kg.

In a similar study using male Slc:Hartley guinea pigs (n = 8) as well, zonisamide showed a significant decrease in the dopamine turnover rate in a dose-dependent manner at all doses tested (10, 30, and 100 mg/kg).

The above results showed that zonisamide dose-dependently suppressed dopamine turnover both in rats (MAO-A is dominant in the striatum) and in guinea pigs (MAO-B is dominant in the striatum), and that the suppressive effect was likely to be more potent in guinea pigs with a higher MAO-B/MAO-A ratio, suggesting that the suppressive effect of zonisamide on dopamine turnover in rats and guinea pigs is exerted based on its MAO-inhibitory effect with relatively higher selectivity for MAO-B.

**(d) Effect on dopamine level in extracellular fluid of rat striatum investigated by brain microdialysis (Data 4.2.1.1-11, 4.2.1.1-12, and 4.2.1.1-13)**

Male Std:Wistar rats (normal rats, n = 8) were implanted with a microdialysis probe into the striatum. Striatal dialysate was collected at 16-minute intervals during 64 minutes before oral administration of zonisamide (10, 30, or 100 mg/kg) or vehicle and during 320 minutes after administration, and subjected to measurement of dopamine content. The total dopamine content in the striatal dialysate collected during the 320 minutes after administration of zonisamide was not significantly different from the content at any dose compared with the vehicle group.

Similarly, when zonisamide (10, 30, or 100 mg/kg) or vehicle was administered orally to normal rats (n = 8), followed by intraperitoneal administration of L-DOPA (100 mg/kg) after 128 minutes, and dopamine content in striatal dialysate was evaluated in a similar manner, the total dopamine content in the dialysate collected during 192 minutes after administration of L-DOPA was not significantly different at any dose compared with the vehicle group.

Unilaterally 6-OHDA-treated rats (n = 8) were implanted with a microdialysis probe into the striatum, and zonisamide (10, 30, or 100 mg/kg) or vehicle was administered orally, followed by intraperitoneal administration of L-DOPA (10 mg/kg) after approximately 2 hours. The dialysate was collected from the striatum of destructive side at 20-minute intervals from 1 hour before dosing of zonisamide until 4 hours after dosing of L-DOPA, and subjected to measurement of dopamine content. Total dopamine content in the dialysate collected up to 4 hours after dosing of L-DOPA increased in a dose-dependent manner, showing a significant increase in the zonisamide 100 mg/kg group compared with the vehicle group.

Thus, zonisamide, either in combination with or without L-DOPA, did not markedly affect dopamine content in the extracellular fluid of the striatum under normal conditions, whereas under conditions where dopamine re-uptake function was lost by destruction of nigrostriatal dopamine neuron, zonisamide enhanced the L-DOPA-induced increase in dopamine content. These results suggested that the activity to increase the dopamine content in the extracellular fluid of the striatum contributes to the antiparkinsonian effect of zonisamide.

### **3.(i).A.(2) Secondary pharmacodynamics**

No new data were submitted.

### **3.(i).A.(3) Safety pharmacology**

No new data were submitted.

### **3.(i).A.(4) Pharmacodynamic drug interactions (Data 4.2.1.4-1)**

#### **3.(i).A.(4).1 Effect of interactions with selegiline, bromocriptine, and amantadine on the enhancement of L-DOPA-induced hyperkinesia**

Reserpine-treated rats were orally administered L-DOPA (200 mg/kg), and locomotor activity was measured every 15 minutes for 210 minutes from immediately after administration. Zonisamide (15 mg/kg) or the vehicle was administered orally at approximately 90 minutes before the start of locomotor activity measurement, and test compounds for interaction (selegiline 5 mg/kg, bromocriptine 1 mg/kg, or amantadine 10 mg/kg) or respective vehicles were administered intraperitoneally immediately before the start of locomotor activity measurement. Administration of zonisamide or each test compound for interaction alone significantly increased the locomotor activity during the period from 90 to 210 minutes (for 120 minutes) after administration of L-DOPA compared with each vehicle. Concomitant use of zonisamide with each test compound further increased the locomotor activity than that observed after administration of zonisamide or each test compound alone. However, results of a two-way layout analysis of variance using zonisamide, test compound, and their interaction as factors did not show significant interaction between zonisamide with any of the test compounds.



Concomitant use of zonisamide with selegiline, bromocriptine, or amantadine (at doses showing moderate enhancing effect) showed an additive effect on L-DOPA-induced hyperkinesia in reserpine-treated rats.

### **3.(i).B Outline of the review by PMDA**

PMDA asked the applicant to explain the reason why, in reserpine-treated rats, the time course pattern of L-DOPA-induced hyperkinesia in the presence of 15 mg/kg of zonisamide, and not in the presence of 50 mg/kg of zonisamide, was more similar to that in the presence of selegiline despite the fact that 50 mg/kg of zonisamide is considered to be more potent in inhibiting MAO activity than 15 mg/kg of zonisamide. PMDA also asked the applicant to explain the observed difference in the effect between zonisamide and selegiline by comparing the effect of zonisamide and selegiline on L-DOPA-induced rotational behavior in unilaterally 6-OHDA-treated rats.

The applicant's response:

Regarding the difference in the mechanism of the antiparkinsonian effect between zonisamide and selegiline, MAO (mainly MAO-B) inhibition contributes to the antiparkinsonian effect of selegiline, whereas the dopamine release-enhancing effect by  $\text{Ca}^{2+}$ -induced exocytosis (*Br J Pharmacol.* 2001;134:507-520) may possibly contribute to the effect of zonisamide in addition to the relatively high MAO-B selective inhibitory effect. In the study using reserpine-treated rats, the time-course pattern of L-DOPA-induced hyperkinesia was similar between the selegiline 5 mg group and the zonisamide 15 mg group but not to the zonisamide 50 mg group. A possible reason for these results is that whereas the MAO-inhibitory effect was dominant in the zonisamide 15 mg/kg group, both MAO-inhibitory effect and dopamine release-enhancing effect may have contributed in the 50 mg/kg group. In the study using unilaterally 6-OHDA-treated rats, unlike selegiline 20 mg/kg (the dose sufficiently inhibiting both MAO-A and MAO-B), zonisamide 100 mg/kg did not increase the total number of rotations and rather tended to decrease the peak rotation numbers. Possible reasons for these observations include: (1) MAO-A and MAO-B were not sufficiently inhibited by zonisamide (100 mg/kg) and (2) the dopamine release-enhancing effect of zonisamide manifested itself in the nondestructive side of dopamine neuron when L-DOPA was administered, resulting in the attenuation of the peak rotational activity toward the nondestructive side.

PMDA asked the applicant to explain the reason why zonisamide dose-dependently enhanced the effect of L-DOPA in nonclinical studies on rats whereas zonisamide dose-dependent improvement in exercise performance was not observed in clinical studies [see Section 4.(ii).A.(1)] and the reason for the difference in the dose response between single- and repeated-dose administrations in monkeys.

The applicant's response:

The differences in the efficacy endpoints in rats and humans may have caused the differences in their dose response. In clinical studies, the primary endpoint was UPDRS Part III which includes, in subsections, items related to higher-order physical function assessable only in humans. Excessive increase in dopamine level induced by zonisamide may have caused dyskinesia, psychiatric symptoms, etc., resulting in an apparent attenuation of the efficacy with dose increase. In rats, in contrast,

dyskinesia-like symptoms occurred only after repeated administration of high-dose methyl L-DOPA (50 mg/kg), and only rarely. Rats were unable to show rotational behavior under this condition, whereas no such symptoms were observed when zonisamide was administered repeatedly. It is difficult to confirm the occurrences of psychiatric symptoms (e.g., hallucination, delusion) in rats and, even if they occurred, they are unlikely to affect the direct endpoints such as locomotor activity and the number of rotations, resulting in the dose response as observed. As for the difference in dose response between single- and repeated-dose administrations in monkeys, the following possibility is plausible: With the increase in the dose of L-DOPA, the pattern of L-DOPA-induced rotational behavior changed from continuous occurrences to periodical increase and decrease in frequency, resulting in attenuation in the effect of L-DOPA (*Life Sciences*. 1986;39:7-16). In addition, increased plasma concentration of zonisamide may lead to an increase in dopamine level. These results suggest that the effect of zonisamide increases with dose increase within a low plasma concentration range whereas it decreases with dose increase within a high plasma concentration range. Thus, it is plausible that repeated administration at a low dose suppressed abrupt increase and decrease in plasma concentration, resulting in the elimination of the risk to reach the plasma concentration range that shows reverse response.

#### PMDA's view:

Results of the primary pharmacodynamic studies suggested the antiparkinsonian effect of zonisamide in animal models in which the effect of conventional antiparkinsonian drugs had been observed, and comparison of the pattern of efficacy manifestation suggested that zonisamide has activities to enhance and prolong the effect of L-DOPA by a mechanism somewhat different from that of drugs in the same class. Although these results suggest that zonisamide exhibits an antiparkinsonian effect by a mechanism different from that of drugs in the same class, explanations of the applicant regarding the mechanism of action of zonisamide lack supporting scientific evidence and are mostly based on assumptions. It is therefore difficult to conclude that suppression of dopamine turnover by MAO inhibition and enhancement of dopamine release are the mechanisms of action of zonisamide in humans, as claimed by the applicant. Also, it is hard to say that the data of nonclinical studies have fully elucidated the mechanism whereby the dose-dependent improvement in physical function is attenuated in humans. Nevertheless, studies on representative animal models of Parkinson's disease have provided results suggesting that the antiparkinsonian effect of zonisamide is based on its effect on dopaminergic neurons. Also, the antiparkinsonian effect of zonisamide has been derived from use experience in clinical settings, and the primary pharmacodynamic studies were not conducted for the purpose of estimating the effect in humans. Therefore, PMDA concluded that it is unnecessary, in proceeding with the review of zonisamide, to require the applicant to conduct an additional efficacy pharmacology study currently.

### **3.(ii) Summary of pharmacokinetic studies**

#### **3.(ii).A Summary of the submitted data**

The applicant submitted data on an additional pharmacokinetic interaction study in the present application.

##### **3.(ii).A.(1) Pharmacokinetic interactions (Data 4.2.2.6-2)**

Zonisamide (30 mg/kg) and L-DOPA (100 mg/body) were administered orally at a single dose to 5 cynomolgus monkeys at 1-week intervals (monotherapy). In addition, zonisamide (30 mg/kg) was

administered orally to 5 cynomolgus monkeys, followed by an oral administration of L-DOPA (100 mg/body) after 2 hours (combination therapy).  $C_{\max}$  of zonisamide was  $23.58 \pm 2.21$   $\mu\text{g/mL}$  (mean  $\pm$  standard error [SE]) and  $25.46 \pm 1.62$   $\mu\text{g/mL}$ , respectively, and the area under plasma drug concentration-time curve (AUC) was  $373.56 \pm 39.47$   $\mu\text{g}\cdot\text{h/mL}$  and  $435.01 \pm 35.06$   $\mu\text{g}\cdot\text{h/mL}$ , respectively, showing no significant difference regardless of concomitant use with L-DOPA.  $C_{\max}$  of L-DOPA was  $9.28 \pm 0.64$  and  $7.89 \pm 0.55$   $\mu\text{g/mL}$ , respectively, and AUC was  $18.71 \pm 0.96$  and  $18.06 \pm 1.15$   $\mu\text{g}\cdot\text{h/mL}$ , respectively, showing no significant difference regardless of concomitant use with zonisamide.

### **3.(ii).B Outline of the review by PMDA**

PMDA considers that there are no particular problems in the newly submitted data. Pharmacokinetic interactions between zonisamide and various antiparkinsonian drugs approved in Japan are discussed in Section 4.(i).B.(3) in the clinical section, together with the necessity of providing cautions.

### **3.(iii) Summary of toxicology studies**

No new data were submitted.

## **4. Clinical data**

### **4.(i) Overview of clinical pharmacokinetics and clinical pharmacology**

#### **4.(i).A Summary of the submitted data**

##### **4.(i).A.(1) BE among formulations**

Tablets used during the development of zonisamide (AD-810N tablets 50 mg, AD-810N tablets 100 mg, Excegran tablets 100 mg, and Trerief Tablets 25 mg) were subjected to investigation of BE.

AD-810N tablets 50 mg and AD-810N tablets 100 mg were used in the phase II study (AD810N-202-1) and in the long-term treatment study (1) (AD810N-203-2). Trerief Tablets were used in the late phase II/phase III study (AD810N-204-5), the phase III study (AD810N-303-8), and the long-term treatment study (2) (AD810N-302-6). AD-810N tablets 50 mg, AD-810N tablets 100 mg, Trerief Tablets, and Excegran Tablets 100 mg were used in the extended treatment study (AD810N-301-4).

##### **4.(i).A.(1).1 BE between Excegran tablets 100 mg and AD-810N tablets 50 mg and between Excegran tablets 100 mg and AD-810N tablets 100 mg (Data 5.3.1.3-1 and 5.3.1.3-2)**

AD-810N tablets 50 mg are [REDACTED] of Excegran Tablets 100 mg, and correspond to Level [REDACTED] in the formulation changes according to the “Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms” (PMSB/ELD Notification No. 64 dated February 14, 2000), and AD-810N tablets 100 mg are the same as Excegran Tablets 100 mg in formulation. Therefore, a dissolution test was conducted according to the “Partial Revision of Guidelines for Bioequivalence Studies of Generic Drugs” (PMSB/ELD Notification No. 786 dated May 31, 2001). Results confirmed the bioequivalence of both formulations.

##### **4.(i).A.(1).2 Japanese BE study on Trerief Tablets and Excegran Tablets 100 mg (1) (Data 5.3.1.2-3, Study AD810N-501-3 [REDACTED] to [REDACTED] 20[REDACTED])**

The difference between Trerief Tablets and Excegran Tablets 100 mg corresponds to Level [REDACTED] according to the “Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms”

(PMSB/ELD Notification No. 64 dated February 14, 2000), and a BE study was conducted in human subjects.

An open-label, two-period, cross-over study was conducted in 10 Japanese healthy adult male subjects (5 per group) with a washout period of  $\geq 21$  and  $< 28$  days, and all of 10 subjects were included in the pharmacokinetic analysis. Following a single oral dose of 100 mg of zonisamide (4 Trerief tablets) under fasting conditions, the geometric mean ratios of  $C_{\max}$  and  $AUC_{0-t}$  of zonisamide following Trerief administration relative to those observed following the administration of the reference formulation (Excegran Tablets 100 mg) was 0.98 to 1.08 and 1.00 to 1.06, respectively, confirming the BE. However, in all subjects in the Stage II of cross-over, the mean plasma zonisamide concentration decreased at 4 to 6 hours after administration and increased again after 8 hours, showing a V-shaped change, while no such phenomenon was observed during the Stage I, with the cause of such change remaining unknown.

**4.(i).A.(1).3 Japanese BE study on Trerief Tablets and Excegran Tablets 100 mg (2) (Data 5.3.1.2-4, Study AD810N-502-7 [20 to 20])**

Although the Japanese BE study (1) described in 4.(i).A.(1).2) above demonstrated the BE between Trerief Tablets and Excegran Tablets, the mean plasma zonisamide concentration showed a V-shaped time course of unknown cause. Therefore, the study was repeated under the same conditions. Two subjects dropped out during the study and, as a result, 8 subjects were included in the pharmacokinetic analysis. The geometric mean ratios of  $C_{\max}$  and  $AUC_{0-t}$  of zonisamide following Trerief administration relative to those observed following the administration of the reference formulation was 0.98 to 1.10 and 0.98 to 1.04, respectively, confirming the BE. The plasma zonisamide concentration did not show V-shaped time-course change.

**4.(i).A.(2) *In vitro* studies using human biomaterials**

**4.(i).A.(2).1 Effect of zonisamide on various cytochrome P-450 (CYP) isoforms (Data 5.3.2.2-2)**

The *in vitro* effect of zonisamide on the metabolism of substrates specific to each human CYP isoform (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4) was investigated using human liver microsomes. Zonisamide at 200  $\mu\text{mol/L}$  (the concentration approximately 10 times higher than the serum zonisamide concentration under steady state [ $C_{ss}$ ] at the dose of 50 mg/day) had little effect on the enzyme activity of any of CYP isoforms. Zonisamide inhibited the enzyme activity of CYP2A6, CYP2C9, CYP2C19, and CYP2E1 concentration-dependently, but the inhibitory rate was approximately 25% even at 600  $\mu\text{mol/L}$  (approximately 30 times the  $C_{ss}$  at the dose of 50 mg/day). Although zonisamide serves as a substrate for CYP3A, the inhibition constant ( $K_i$ ) of zonisamide against CYP3A4 is 1076  $\mu\text{mol/L}$ , which is  $\geq 50$  times the  $C_{ss}$  at the dose of 50 mg/day, suggesting that the inhibitory activity is of little clinical significance.

**4.(i).A.(2).2 Effect of zonisamide on the metabolism of antiparkinsonian drugs (Data 5.3.2.2.-1)**

The *in vitro* effect of zonisamide on the metabolism of conventional antiparkinsonian drugs (biperiden hydrochloride, bromocriptine, selegiline, and talipexole hydrochloride) was investigated using human liver microsomes. The rate of metabolism of these drugs by human liver microsomes was not affected by zonisamide (40, 200, and 1000  $\mu\text{mol/L}$ , which were approximately 2 to 50 times the  $C_{ss}$  at the dose of 50 mg/day).

#### 4.(i).A.(3) Clinical pharmacokinetics

The applicant submitted pharmacokinetics evaluation data from a phase II study and a long-term treatment study (1), and reference data from a foreign clinical study in patients with hepatic impairment and 4 studies on drug-drug interactions.

##### 4.(i).A.(3).1) Pharmacokinetics in patients with Parkinson's disease

###### (a) Phase II study (Data 5.3.4.2-1, Study AD810-SR-00009 (AD801N-202-1) [■ 20■ to ■ 20■])

Zonisamide (50 or 100 mg) was administered once daily for 2 weeks to patients with Parkinson's disease who were taking L-DOPA preparation, followed by administration of zonisamide (50, 100, or 200 mg) once daily for 8 weeks. Serum zonisamide concentration was measured at baseline and 2, 6, and 10 weeks after the start of administration (or at study discontinuation). Population pharmacokinetic analysis was performed using serum concentration data at 252 points obtained from 90 patients. The characteristics of 90 patients were 38 males and 52 females, 62.5 years old in mean age (minimum-maximum, 39-79), 54.3 kg (33.0-77.0 kg) in mean body weight, and 73.5 mL/min (38.7-138 mL/min) in mean creatinine clearance. Pharmacokinetics after multiple administration of zonisamide was analyzed using a 1-compartment model, with medical institution, dose, sex, age, height, body weight, body mass index (BMI), concomitant drugs, and laboratory test values as variable factors. As a result, the effect of body weight on clearance (CL/F) and on distribution volume (Vd/F) was observed. Inter- and intra-individual variability of CL/F was modeled as proportional error models. The final model and coefficient of variation (CV) of inter- and intra-individual variability are as follows:

$$CL/F \text{ (L/h)} = 0.0117 \times 54 \times (WT/54)^{0.579} \times \exp(\eta_{CL/F}),$$

$$Vd/F \text{ (L)} = 0.964 \times 54 \times (WT/54)^{0.579}$$

Where, WT is body weight (kg) and  $\eta_{CL/F}$  is inter-individual variability of CL/F (difference in parameter value between each subject and the population parameter value)

Inter-individual variability of CL/F (CV%), 31.2%

Intra-individual variability of residue (CV%), 18.3%

Observed value of  $C_{ss}$  was proportional to dose; the value was  $3.5 \pm 1.4 \mu\text{g/mL}$  in administration of 50 mg (mean  $\pm$  SD of 125 samples from 63 subjects).  $C_{ss}$  estimate calculated from estimated parameter values in each subject was also proportional to dose.

In contrast, no correlation was observed between serum zonisamide concentration and changes in total UPDRS Part II (ON time and OFF time) or in total Part III score, efficacy endpoints.

###### (b) Long-term treatment study (1) (Data 5.3.4.2-2, Study AD810-SR-00018 (AD801-203-2) [■ 20■ to ■ 20■])

Zonisamide (50 mg) was administered once daily for 2 to 4 weeks to patients with Parkinson's disease who had completed the phase II study described in 4.(i).A.(3).1).(a) above, followed by administration of zonisamide (50-200 mg) once daily for 48 to 54 weeks. Serum zonisamide concentration was measured at baseline, and 4, 8, 16, 28, 40, and 52 to 56 weeks after administration, or at study discontinuation, whenever possible. Serum concentration data at 179 points were obtained from 37 patients. The following table shows the observed values of serum zonisamide concentration in this study,

which were similar to those obtained in the phase II study. The data were fitted to the population pharmacokinetics model constructed in the phase II study, and CL/F in each patient was calculated from the observed values of each patient by Bayesian estimation. Results showed that the CL/F remained almost at a constant level throughout the treatment period.

In contrast, no correlation was observed between serum zonisamide concentration and changes in total UPDRS Part II (ON time and OFF time) or total Part III score, efficacy endpoints.

**Table. Serum zonisamide concentration**

Dose (mg/day)	After 4 weeks (Day 25-31)	After 8 weeks (Week 7-9)	After 16 weeks (Week 15-17)	After 28 weeks (Week 27-29)	After 40 weeks (Week 39-41)	After 52 weeks (Week 52-57)
50	3.0 ± 1.5 <sup>a</sup> (16)	3.1 ± 1.3 (6)	4.3 ± 2.8 (8)	4.6 ± 2.1 (5)	4.2 ± 1.9 (5)	2.5 ± 1.1 (5)
100	6.8 ± 2.7 (15)	6.8 ± 2.0 (17)	6.9 ± 2.2 (14)	6.4 ± 3.0 (11)	7.5 ± 3.3 (12)	8.7 ± 2.6 (8)
150	10.7 ± 7.0 (3)	15.4 ± 5.1 (5)	13.9 ± 5.4 (6)	15.6 ± 3.9 (4)	12.3 ± 0.2 (2)	12.3 (1)
200	15.7 (1)	13.4 ± 3.4 (7)	14.2 ± 3.4 (5)	15.0 ± 4.1 (6)	16.3 ± 3.0 (6)	15.7 ± 4.0 (6)

a Mean ± SD (µg/mL). The number in the parentheses denotes the number of patients.

#### **4.(i).A.(3).2) Pharmacokinetics in patients with hepatic impairment (Reference data) (Data 5.3.3.3-2, Study RR-MEMO-764-01123)**

Following a single oral administration of zonisamide (300 mg) to 2 non-Japanese patients with alcoholic liver cirrhosis,  $C_{max}$  was 2.15 and 2.70 µg/mL,  $T_{max}$  was 3 and 9 hours,  $T_{1/2}$  was approximately 57 and 84 hours, and the area under the concentration-time curve until infinity ( $AUC_{\infty}$ ) was 196.7 and 305.0 µg·h/mL respectively. These parameter values were within the range observed when zonisamide (300 mg) was administered to non-Japanese healthy adults ( $C_{max}$ , 1.90-7.93 µg/mL;  $T_{max}$ , 1.0-9.0 hours;  $T_{1/2}$ , 28.7-86.5 hours;  $AUC_{\infty}$ , 186-339 µg·h/mL) (Study RR 764-00458).

#### **4.(i).A.(3).3) Drug-drug interaction studies**

##### **(a) Interaction with cimetidine (Reference data) (Data 5.3.3.4-2, Study RR-764-00605)**

The effect of concomitant use with cimetidine on plasma zonisamide concentration following a single oral administration of zonisamide (300 mg) was investigated in 8 non-Japanese healthy adults (4 per group) using a two-treatment cross-over design. Cimetidine was administered orally at a dose of 300 mg 4 times daily from 4 days before until 9 days after administration of zonisamide. Plasma zonisamide concentration parameters following the administration of zonisamide alone and in combination with cimetidine were as follows:  $C_{max}$ , 3.42 and 3.37 µg/mL;  $T_{1/2}$ , 60 and 66 hours;  $AUC_{\infty}$ , 272 and 290 µg·h/mL; and CL/F, 0.241 and 0.228 mL/min/kg, respectively. Thus, the pharmacokinetic parameters of zonisamide were not affected by concomitant use with cimetidine.

##### **(b) Interaction with ketoconazole (Reference data) (Data 5.3.3.4-3, Study ■■■46046-109)**

A single dose of zonisamide (100 mg) was administered orally to 17 non-Japanese healthy adults (Period 1). Then, a single dose of zonisamide (100 mg) was administered orally during the 12-day multiple oral administration of ketoconazole (400 mg once daily from 2 days before administration of zonisamide) (Period 2). Plasma zonisamide concentration in these subjects was measured. The interval between

Period 1 and Period 2 was 10 days. Parameter values of zonisamide in Period 1 and Period 2 were as follows:  $C_{\max}$ ,  $1.059 \pm 0.3054$  and  $1.107 \pm 0.2479$   $\mu\text{g/mL}$  (mean  $\pm$  SD);  $T_{\max}$ ,  $3.2 \pm 1.13$  and  $6.1 \pm 5.08$  hours;  $T_{1/2}$ ,  $75.2 \pm 17.08$  and  $69.6 \pm 16.94$  hours; and the area under the concentration-time curve until the time of the final measurable concentration ( $\text{AUC}_{\text{last}}$ ),  $80.9 \pm 20.35$  and  $96.6 \pm 20.95$   $\mu\text{g}\cdot\text{h/mL}$ , respectively. The 90% confidence interval of the geometric mean ratio of  $\text{AUC}_{\text{last}}$  was 1.12 to 1.29, indicating that concomitant use with ketoconazole slightly increased  $\text{AUC}_{\text{last}}$  of zonisamide. Zonisamide was detected in plasma in a majority of subjects immediately before proceeding to Period 2. When pharmacokinetic parameters were calculated after subtracting the carry-over from Period 1 (5%-10%), the 90% confidence interval of the geometric mean ratio of  $\text{AUC}_{\text{last}}$  was 1.06 to 1.22.

These results showed that the effect of ketoconazole on the kinetics in blood is insignificant, suggesting that it is unnecessary to adjust the dose of zonisamide in combination with ketoconazole or other CYP3A inhibitors.

**(c) Interaction with phenobarbital (Reference data) (Data 5.3.3.4-4, Study RR-764-00616)**

Zonisamide (300 mg) was administered orally to 8 non-Japanese healthy adults and, on Day 22 after the start of multiple oral administration of phenobarbital (90 mg/day), zonisamide was concomitantly administered.  $C_{\max}$  and  $T_{\max}$  of zonisamide were not affected by concomitant use with phenobarbital. In contrast, the concomitant use caused a decrease in  $T_{1/2}$  from 58.0 to 38.0 hours (66%), a significant decrease in  $\text{AUC}_{\infty}$  from 238 to 161  $\mu\text{g}\cdot\text{h/mL}$  (68%), and an increase in  $\text{CL/F}$  after oral administration from 0.271 to 0.402  $\text{mL/min/kg}$  (148%). The urinary excretion rate of the unchanged zonisamide decreased from 17.0% to 9.5% (0.56-fold).

These results suggested that multiple administration of phenobarbital significantly increases  $\text{CL/F}$  of zonisamide.

**(d) Interaction with phenytoin (Reference data) (Data 5.3.3.4-5, Study RR-720-00900)**

A single dose of zonisamide (400 mg) was administered orally to 6 non-Japanese patients with epilepsy who had been in stable conditions for  $\geq 1$  month by administration of phenytoin (400-650 mg/day), and the pharmacokinetics of zonisamide in combination with phenytoin was investigated. The plasma zonisamide concentration reached  $C_{\max}$  (4.8  $\mu\text{g/mL}$ ) at 2.5 hours after administration, after which zonisamide was eliminated with  $T_{1/2}$  of 27.1 hours.  $\text{CL/F}$  was 0.565  $\text{mL/min/kg}$ . Compared with the values observed following the oral administration of zonisamide alone, described in above 4.(i).A.(3).3).(a) and 4.(i).A.(3).3).(c),  $T_{1/2}$  was shorter and  $\text{CL/F}$  was greater.

**(e) Interaction with carbamazepine (Reference data) (Data 5.3.3.4-6, Study RR-720-02212)**

A single dose of zonisamide (400 mg) was administered orally to 6 non-Japanese patients with epilepsy who had been in stable conditions for  $\geq 1$  month by administration of carbamazepine (500-1400 mg/day), and the pharmacokinetics of zonisamide in combination with carbamazepine was investigated.  $C_{\max}$  of zonisamide in plasma was 5.1  $\mu\text{g/mL}$ ,  $T_{1/2}$  was 37.6 hours,  $\text{AUC}_{\infty}$  was 268  $\mu\text{g}\cdot\text{h/mL}$ , and  $\text{CL/F}$  was 21.2  $\text{mL/h/kg}$  (0.353  $\text{mL/min/kg}$ ). Compared with the values observed following the oral administration of zonisamide alone, described in above 4.(i).A.(3).3).(a) and 4.(i).A.(3).3).(c),  $T_{1/2}$  was shorter and  $\text{CL/F}$  was greater.

#### **4.(i).B Outline of the review by PMDA**

Although the proposed dosage and administration was 25 to 50 mg/day, no pharmacokinetic study was conducted at low doses below 50 mg/day at the application. PMDA thus reviewed the data by focusing on the following points.

##### **4.(i).B.(1) Pharmacokinetics at the clinical doses**

PMDA asked the applicant to explain the appropriateness of interpreting the pharmacokinetics of zonisamide over the proposed dose range of 25 to 50 mg based on the results obtained from the study at a different dose range (100-400 mg).

The applicant's response:

Results of the phase I clinical studies (single- and multiple-dose administrations, data F-8 and G-1 submitted for the previous approval) and the BE study [see Section 4.(i).A.(1).2) and 4.(i).A.(1).3)], both involving healthy adults, showed that  $C_{\max}$  and AUC were roughly correlated with dose (100-400 mg),  $T_{1/2}$  was generally within the range from 50 to 90 hours, and  $T_{1/2}$  did not increase with dose. In the phase II study in patients with Parkinson's disease, a correlation was observed between the dose and  $C_{ss}$  over the dose range from 50 to 200 mg/day (serum concentration  $\leq 30$   $\mu\text{g/mL}$ ). If one supposes that the lack of dose-dependency within the zonisamide dose range of 25 to 50 mg/day [see Section 4.(ii).A.(2) and 4.(ii).A.(3)] was caused by the non-linearity of the pharmacokinetics, then plasma zonisamide concentration achieved at doses lower than 50 mg would have been higher than the level expected from the dose-proportional response. However, the inspection of the non-linear processes in absorption, distribution, and CL/F showed it unlikely that, following the administration at doses below 50 mg, the plasma zonisamide reaches a level higher than that expected from the dose-proportional response in any of these processes. Therefore, based on the results of the study on the dose range (100-400 mg) investigated at the approval of Excegran and on the dose range (50-200 mg) investigated in patients with Parkinson's disease, the applicant determined that it is appropriate to extrapolate the above data to estimate the pharmacokinetics of zonisamide over the dose range from 25 to 50 mg in patients with Parkinson's disease by assuming the dose-proportional response.

PMDA asked the applicant to explain the reason that the mean  $C_{ss}$  (2.5-4.6  $\mu\text{g/mL}$ ) at Week 4 to 52 in multiple administration of zonisamide (50 mg) to patients with Parkinson's disease increased to a level similar to the  $C_{\max}$  observed following a single-dose administration at 300 mg to non-Japanese patients with normal renal function and to healthy adults (3.64 and 3.31-3.88  $\mu\text{g/mL}$ , respectively; data F-9 and 10 submitted for the previous approval, Reference data 5.3.3.3-2, 5.3.3.4-1). PMDA also asked the applicant to discuss the possibility of increase in serum zonisamide concentration with the increase in the treatment period, judging from the changes over time in the serum zonisamide concentration in individual patients in the phase II study.

The applicant's response:

The accumulation ratio calculated from the mean  $T_{1/2}$  (approximately 50 hours) and the maximum  $T_{1/2}$  (approximately 90 hours) in healthy adults receiving a single dose of zonisamide (300 mg) (Reference data 5.3.3.3-2) is approximately 3.5 and 5.9, respectively, which suggests it appropriate to assume that



$C_{ss}$  after multiple administration at 50 mg in patients with Parkinson's disease is similar to the  $C_{max}$  following a single-dose administration at 300 mg, 6 times the dose. As for the possible increase in serum zonisamide concentration with the increase in the treatment period, the serum concentration is expected to remain almost at a constant level without such an increase over the long-term treatment period, judging from the observations that (1) in the phase II study, the mean serum zonisamide concentration was not different at 2, 6, and 10 weeks after the start of multiple administration, and the time-course change in the serum concentration was similar among subjects, and that (2) the serum zonisamide concentration in the long-term treatment study (1) in patients with Parkinson's disease receiving zonisamide again after completion of the phase II study was similar to that observed in the phase II study.

PMDA's view:

Since the proposed dose is widely different from the approved dose (only approximately one-eighth times), the applicant should have conducted a pharmacokinetic study within the dose range 25 to 50 mg before the submission of application. However, a food effect study is currently ongoing, which is expected to provide useful information on the pharmacokinetics in single-dose administration at 25 mg. Appropriateness of not conducting a pharmacokinetic study in patients with Parkinson's disease over the pertinent dose range is discussed in the following section.

#### **4.(i).B.(2) Zonisamide dose viewed from the relationship between pharmacokinetics and efficacy in patients with Parkinson's disease**

The relationship between blood zonisamide concentration and efficacy was discussed based on the investigation within the range from 50 to 200 mg/day in the phase II study, but no such discussion was made on the relationship at doses below 50 mg. Therefore, PMDA asked the applicant to explain the relationship between blood zonisamide concentration and efficacy over the range from 25 to 50 mg.

The applicant's explanation:

The absolute change in the UPDRS Part III total score at zonisamide dose of 25 to 50 mg was greater than that observed at higher doses (high concentration range), which suggests that there is an optimum blood concentration range in each subject and the range varies from subject to subject. Since it was determined that there is a difference in the blood zonisamide concentration (exposure) between administration of 25 mg and administration of 50 mg according to the difference in the dose, the lack of the difference in the efficacy between the 25 and 50 mg groups in the late phase II/phase III study and the phase III study is not considered to be due to the similar blood concentration (exposure). On the other hand, as for the lack of clear difference in the efficacy between the 25 and 50 mg groups, it is conceivable that both doses are close to the range exhibiting the maximum efficacy, with the dose (blood concentration)-efficacy curve reaching a plateau. Also, since it is suspected that the response to zonisamide and the optimal blood concentration differ among individual subjects, obtained data may have scattered irregularly instead of gathering to a focus. It is considered that, at the blood concentration range produced by 25 to 50 mg of zonisamide, the efficacy reaches the maximum level, with the concentration-efficacy curve becoming a plateau.

PMDA asked the applicant to clarify the relationship between the mechanism of action of zonisamide and UPDRS score and, upon this clarification, to explain the appropriateness of comparing UPDRS

score and blood zonisamide concentration measured at an arbitrary single blood sampling point after administration of zonisamide.

The applicant's response:

Zonisamide is considered to enhance or prolong the action of L-DOPA by inhibiting MAO and enhancing dopamine release. Thus, zonisamide does not exert its effect directly in blood; instead, it is transferred into brain where it inhibits MAO and enhances dopamine release. As an overall result of these effects and biological reactions, UPDRS Part III scores, indices for the motor activity of patients, change. Zonisamide has a long elimination half-life with  $T_{1/2}$  of approximately 50 hours on average and 90 hours at the maximum. When multiple dose of zonisamide is administered to healthy adults once daily at 200 mg, the ratio of the peak concentration (11.7 µg/mL) to the trough concentration (9.7 µg/mL) is 1.2. Thus, the peak concentration, the mean concentration (calculated by dividing AUC under steady state by dosing interval), and the trough concentration are similar to one another. As a result, when the correlation between blood zonisamide concentration and efficacy is investigated, similar results will be obtained regardless of the type of blood concentration used, whether it be observed blood concentration, estimated concentration at each time of score evaluation, peak concentration, mean concentration, or trough concentration. It is considered appropriate to use, in comparing with UPDRS scores, directly observed blood concentrations rather than those estimated by various methods.

PMDA's view:

It is difficult to explain the effect of zonisamide solely from MAO inhibition and dopamine release enhancement. Although results of pharmacological studies suggest the pharmacological effects of zonisamide (MAO inhibition and dopamine release enhancement), they are not directly confirmed in humans. In addition, blood zonisamide concentration was not measured in the phase III study comparing the efficacy and safety between placebo and zonisamide (25 and 50 mg). Thus, there is little evidence available to discuss the relationship between blood zonisamide concentration and efficacy. As a result, it is unclear whether the failure of dose increase from 25 to 50 mg to achieve an increase in the efficacy is due to the saturation of the efficacy or to attenuation of the efficacy for some reason or other. Also, it is unclear how effective zonisamide is at doses below 25 mg. Although pharmacokinetics of zonisamide in patients at clinical doses (except 50 mg) has not been investigated, PMDA concluded that this does not pose any clinically significant problem, taking account of the facts that the proposed doses are lower than the approved dose and that no adverse events of clinical concern were observed at 25 mg. Necessity of the dose 50 mg is discussed in Section "4.(ii).B.(4) Dosage and administration," also taking account of the lack of data on the extent of increase in blood concentration (exposure) at 50 mg relative to 25 mg and on the relationship between the increase in the blood concentration (exposure) and efficacy.

#### **4.(i).B.(3) Drug-drug interactions**

Drug-drug interactions in combination with CYP3A4 inducers or inhibitors were investigated within zonisamide dose range of 100 to 400 mg. Therefore, PMDA asked the applicant to explain the effect of the concomitant use with CYP3A4 inducers or inhibitors on the pharmacokinetics of zonisamide at a dose of 25 to 50 mg and on the efficacy and safety of zonisamide.

The applicant's response:

Concomitant use with CYP3A4 inducers (phenobarbital, phenytoin, or carbamazepine) causes an increase in the amount of CYP3A4, resulting in an increase in the metabolic clearance of zonisamide. The doses of zonisamide used in the drug interaction studies were within the dose range that shows linear pharmacokinetics without saturation of metabolic clearance when administered alone, which suggests that the effect of CYP3A4 inducers on metabolic clearance at 25 to 50 mg of zonisamide is similar to that observed in these studies. On the other hand, studies on the effect of CYP3A4 inhibitors cimetidine and ketoconazole on the pharmacokinetics of zonisamide showed that cimetidine did not cause any significant change and ketoconazole had no major effect. Since the inhibitors had no effect on metabolic clearance even at high doses of zonisamide susceptible to such an effect, it is considered that they have little effect over the dose range from 25 to 50 mg as well.

Thus, although concomitant use of CYP3A4 inducers with zonisamide may slightly decrease  $C_{ss}$  of zonisamide, possibly affecting the efficacy, there is no safety problem. On the other hand, concomitant use of CYP3A4 inhibitors with zonisamide is expected not to have any clinically significant effect, either in efficacy or in safety.

PMDA accepted the explanation of the applicant taking account of the following: (1) The proposed doses are lower than the approved doses and are unlikely to pose safety problems, judging from the extent of the effect of CYP3A4 inhibitors observed in drug-drug interaction studies conducted at higher doses, and cautions are provided in the "Precautions for concomitant use" section of the package insert (proposed) that "It is suggested that phenytoin, carbamazepine, and phenobarbital induce CYP, decreasing blood zonisamide concentration."

Since zonisamide is intended to be used in combination with other antiparkinsonian drugs, PMDA asked the applicant to explain their view on the necessity of providing cautions, upon examining possible pharmacokinetic interactions between zonisamide and approved antiparkinsonian drugs based on the data from nonclinical and clinical studies, published reports, and others.

The applicant's response:

1) Possible effect of zonisamide on the pharmacokinetics of antiparkinsonian drugs

(a) L-DOPA preparations

Pharmacokinetic interactions between zonisamide and L-DOPA were investigated using cynomolgus monkeys [see Section 3.(ii).A.(1)]. Results showed no pharmacokinetic interactions between these drugs, suggesting that zonisamide does not affect the plasma L-DOPA concentration in clinical settings.

(b) Dopamine agonists

Dopamine agonists approved in Japan include ergot alkaloids bromocriptine, cabergoline, and pergolide as well as non-ergot dopamine agonists ropinirole, talipexole, and pramipexole. Bromocriptine and cabergoline are metabolized by CYP3A4, and ropinirole mainly by CYP1A2 (partly by CYP3A4), but zonisamide does not have a clinically significant inhibitory effect against CYP3A4 or CYP1A2 [see Section 4.(i).A.(2).1)]. As for pergolide, talipexole, and pramipexole, there are no reports of concomitant drugs inhibiting their metabolism and thereby affecting pharmacokinetics. In *in vitro* studies using

human liver microsomes, zonisamide did not affect the metabolism of bromocriptine or talipexole, nor did it induce CYP3A4 in clinical settings [see Section 4.(i).A.(2).2)]. These results suggest that zonisamide is unlikely to induce pharmacokinetic interactions with dopamine agonists either by metabolic inhibition or by enzyme induction.

Pergolide shows a high protein binding rate of  $\geq 90\%$ , requiring caution in combination of drugs with a high protein binding rate. However, the binding rate of zonisamide to human serum proteins is low, at 48.6%, and does not show interaction with other drugs (sultiame, phenytoin, or phenobarbital) in protein binding. These results suggest that zonisamide is unlikely to affect the protein binding of pergolide.

Renal clearance of pramipexole is shown to decrease when concomitantly administered with cimetidine and amantadine, drugs excreted from kidney via the cation transport system. Whether urinary excretion of zonisamide is mediated by the cation transport system is not studied or reported. However, in light of observation that concomitant use with cimetidine does not cause any significant change in the pharmacokinetics of zonisamide, it is unlikely that zonisamide causes drug-drug interactions through the cation transport system.

(c) MAO-B inhibitors

Selegiline is metabolized by CYP2D6 and CYP3A4, whereas, in the *in vitro* study using human liver microsomes, it has been shown that zonisamide does not affect the metabolism of selegiline, nor does it inhibit either CYP2D6 or CYP3A4 [see Section 4.(i).A.(2).1) and 4.(i).A.(2).2)]. It is therefore unlikely that interaction occurs between zonisamide and selegiline.

(d) Anticholinergic drugs

The package inserts of anticholinergic drugs (trihexyphenidyl, profenamine, biperiden, metixene, piroheptine, and mazaticol) and a published report (*Clin Pharmacokinet.* 2002;41:261-309) do not contain a description of precautions for pharmacokinetic interactions mediated by metabolic inhibition or protein binding. Among these drugs, biperiden was subjected to an *in vitro* study on the susceptibility of its metabolism to the effect of zonisamide. Results confirmed that zonisamide does not affect the metabolism of biperiden [see Section 4.(i).A.(2).2)].

(e) Amantadine

Approximately 70% of amantadine administered is excreted in urine in the form of the unchanged amantadine within 48 hours administration, raising a possibility that blood concentration is increased by concomitant use with drugs that decrease renal excretion of amantadine (thiazide diuretics) (*Clin Pharmacokinet.* 2002;41:261-309). In contrast, there is no report of zonisamide inhibiting renal excretion of other drugs, suggesting that concomitant use of zonisamide with amantadine does not affect renal excretion of amantadine.

(f) Droxidopa

The rate of binding of droxidopa to human serum proteins is low, at approximately 22%, suggesting that it is unlikely to interact with zonisamide when concomitantly administered [see (b) in this section].

There is no report of change in droxidopa metabolism caused by concomitant use with other drugs, suggesting that concomitant use of zonisamide is unlikely to affect the pharmacokinetics of droxidopa.

(g) Catechol-O-methyltransferase (COMT) inhibitor

The plasma protein binding of entacapone is approximately 98%, but zonisamide is unlikely to interact with entacapone, as is the case discussed in this section (b) above. Also, entacapone is metabolized through isomerization to Z form and glucuronidation, and does not undergo CYP-catalyzed metabolism, suggesting that zonisamide is unlikely to affect the metabolism of entacapone.

2) Possible effects of antiparkinsonian drugs on the pharmacokinetics of zonisamide

Ergot alkaloids bromocriptine and pergolide inhibit CYP3A4 *in vitro*, and cabergoline is suggested to have CYP3A4-inhibitory activity (*Clin Ther.* 2006;28:1065-1078). Although CYP3A4 is involved in the metabolism of zonisamide, CYP3A4 inhibitors cimetidine and ketoconazole had no significant effect on the pharmacokinetics of zonisamide. These results suggest that concomitant use with bromocriptine, pergolide, or cabergoline would not affect the pharmacokinetics of zonisamide.

The effect of concomitant antiparkinsonian drugs on the pharmacokinetics of zonisamide was investigated in the phase II study by population pharmacokinetic analysis. No significant parameters were obtained for concomitant antiparkinsonian drugs, suggesting that concomitant antiparkinsonian drugs is unlikely to affect the pharmacokinetics of zonisamide [see Section 4.(i).A.(3).1)].

The above results, taken together, suggest that concomitant use of zonisamide with antiparkinsonian drugs approved in Japan is unlikely to cause pharmacokinetic interactions, thus cautionary advice is not necessary.

PMDA considers that information on the safety of zonisamide concomitantly administered with antiparkinsonian drugs should be collected after the market launch [see Section 4.(ii).B.(6).3)], but accepted the response of the applicant, based on the conclusion that pharmacokinetic interactions are unlikely to occur between zonisamide and other antiparkinsonian drugs.

**4.(i).B.(4) Food effect**

No food effect study was conducted using the final drug product for the present application. In the food effect study conducted for the prior application of the approved indications, zonisamide was administered at 6 to 12 times the dose proposed in the present application. Taking account of the above, PMDA asked the applicant to conduct a food effect study using the final drug product.

The applicant agreed to confirm the food effect in a clinical study using the final drug product.

A study to investigate the food effect on the final drug product (one 25 mg-tablet administration) in healthy adults is currently ongoing, and results will be reviewed in Review Report (2).

#### **4.(i).B.(5) BE study**

The applicant had determined that the V-shaped time-course curve of plasma zonisamide concentration observed in the Japanese BE study (1) (AD810N-501-3) is not an intrinsic but an accidental phenomenon. PMDA accepted the explanation of the applicant based on the data of other pharmacokinetic studies as well, and concluded that it is appropriate to conclude the BE of Terief Tablets 25 mg with Excegran Tablets 100 mg based on the results of the Japanese BE study (2) (AD810N-502-7).

#### **4.(ii) Summary of clinical efficacy and safety**

##### **4.(ii).A Summary of the submitted data**

The applicant submitted evaluation data from 1 phase II study (AD810N-202-1), 1 late phase II/phase III study (AD810N-204-5), and 2 long-term treatment studies (AD810N-203-2 and AD810N-302-6), all conducted in Japan. The applicant also submitted the data of 1 additional phase III study (AD810N-303-8) which was conducted during the review process. The applicant also submitted reference data from an extended treatment study (AD810N-301-4 [ongoing]), an extension from the late phase II/phase III study, a long-term treatment study, and a phase III study.

##### **4.(ii).A.(1) Phase II study (Data 5.3.5.1-1, Study AD810N-202-1 [■ 20■ to ■ 20■])**

A randomized, double-blind study was conducted to investigate the efficacy and safety of zonisamide in an exploratory manner in patients with Parkinson's disease who have not responded sufficiently to L-DOPA preparation (including combination drug L-DOPA/DCI) (target sample size, 120 subjects [30 per group]) in 26 study sites in Japan. The administration period, which followed a 2-week run-in period, consisted of a 2-week trial-run period, an 8-week treatment period, and a 2-week dose reduction period. During the treatment period, zonisamide (50, 100, or 200 mg) or placebo was administered orally once daily. During the trial-run period and the dose reduction period, zonisamide was administered orally once daily at half the dose used in the treatment period (in the 50 mg group, 50 mg was administered without dose reduction to half).

The main inclusion criteria were patients aged  $\geq 20$  and  $< 80$  years with a history of treatment with L-DOPA preparation for  $\geq 6$  months who responded to the treatment from the beginning of the treatment which had been given without change in the dosage regimen from  $\geq 4$  weeks before the start of the run-in period, and met either of the following criteria: (a) Patients showing wearing-off phenomenon, (b) patients showing attenuation of the effect of L-DOPA preparation, and (c) patients who were hesitating to increase the dose of L-DOPA because of adverse drug reactions. The patients also had to be able to record the changes of symptoms in the diary by themselves.

Concomitant use of zonisamide preparation, other unapproved drugs, or other study drugs was prohibited. L-DOPA preparation should be administered without change in the dosage regimen throughout the study period from 4 weeks before the run-in period. The same rule as that applied to L-DOPA preparation was applied also to antiparkinsonian drugs other than L-DOPA preparation and to antihypertensive drugs, neuropsychiatric drugs, etc., that may affect the symptoms of Parkinson's disease.

A total of 136 randomized patients (34 in the zonisamide 50 mg group, 36 in the 100 mg group, 34 in the 200 mg group, and 32 in the placebo group) were included in the safety analysis. Of them, 4 patients who discontinued the study during the trial-run period were excluded because of the “missing data during the period other than the trial-run period,” and the 132 patients (33 patients, 36 patients, 32 patients, 31 patients) who were transitioned to the treatment period were included in the full analysis set (FAS). A total of 124 patients (31 patients, 32 patients, 30 patients, 31 patients) among the 132 patients, excluding 4 patients with violation of concomitant drugs/therapies, 3 patients with insufficient treatment period, 2 patients with violation of exclusion criteria, and 2 patients with noncompliance (including duplicate counting), were included in the per protocol set (PPS) and subjected to the primary efficacy analysis.

Among efficacy endpoints, the change in the UPDRS Part III total score at the final assessment (at the end or discontinuation of the treatment period) from baseline (immediately before the start of administration) was  $-9.2 \pm 1.4$  (least squares mean  $\pm$  SE; analysis of covariance [ANCOVA] with treatment group as factor and baseline value as covariate) in the 50 mg group,  $-6.5 \pm 1.3$  in the 100 mg group,  $-6.4 \pm 1.4$  in the 200 mg group, and  $-3.6 \pm 1.4$  in the placebo group. The change in ON time at the final assessment from baseline (immediately before the start of administration) in patients showing wearing-off phenomenon was  $1.3 \pm 3.3$  (mean  $\pm$  SD) in the 50 mg group,  $0.5 \pm 2.9$  in the 100 mg group,  $1.3 \pm 2.6$  in the 200 mg group, and  $0.7 \pm 2.1$  in the placebo group.

As for safety, the incidence and the number of adverse events were 76.5% (26 of 34) of patients (126 events) in the 50 mg group, 86.1% (31 of 36) of patients (177 events) in the 100 mg group, 97.1% (33 of 34) of patients (158 events) in the 200 mg group, and 84.4% (27 of 32) of patients (117 events) in the placebo group. The following table shows adverse events reported by  $\geq 5\%$  of patients receiving zonisamide. No death occurred, whereas serious adverse events were observed in 8.8% (3 of 34) of patients in the 50 mg group (ventricular extrasystoles, suspected neuroleptic malignant syndrome, and granulocyte count decreased/white blood cell count decreased in 1 patient each), 8.3% (3 of 36) of patients in the 100 mg group (delirium, neutropenia, and hallucination/delusion in 1 patient each), 5.9% (2 of 34) of patients in the 200 mg group (aspiration and neuroleptic malignant syndrome in 1 patient each), whereas no serious adverse event was observed in the placebo group.

**Table. Adverse events reported by  $\geq 5\%$  of patients receiving zonisamide**

	50 mg (N = 34)	100 mg (N = 36)	200 mg (N = 34)	Placebo (N = 32)	Zonisamide combined (N = 104)
Nausea	23.5% (8)	13.9% (5)	17.6% (6)	12.5% (4)	18.3% (19)
Somnolence	17.6% (6)	41.7% (15)	20.6% (7)	18.8% (6)	26.9% (28)
Inappetence	17.6% (6)	16.7% (6)	29.4% (10)	9.4% (3)	21.2% (22)
Nasopharyngitis	17.6% (6)	8.3% (3)	8.8% (3)	3.1% (1)	11.5% (12)
Stomach discomfort	14.7% (5)	8.3% (3)	23.5% (8)	9.4% (3)	15.4% (16)
Thirst	11.8% (4)	27.8% (10)	23.5% (8)	18.8% (6)	21.2% (22)
Headache	11.8% (4)	22.2% (8)	17.6% (6)	12.5% (4)	17.3% (18)
Blood CK increased	11.8% (4)	11.1% (4)	2.9% (1)	9.4% (3)	8.7% (9)
Stumbling	11.8% (4)	8.3% (3)	14.7% (5)	12.5% (4)	11.5% (12)
Constipation	8.8% (3)	13.9% (5)	14.7% (5)	9.4% (3)	12.5% (13)
Palpitations	8.8% (3)	11.1% (4)	14.7% (5)	6.3% (2)	11.5% (12)
Dizziness postural	8.8% (3)	8.3% (3)	5.9% (2)	3.1% (1)	7.7% (8)
Insomnia	5.9% (2)	27.8% (10)	11.8% (4)	9.4% (3)	15.4% (16)
Malaise	5.9% (2)	22.2% (8)	11.8% (4)	15.6% (5)	13.5% (14)
Hallucination	5.9% (2)	8.3% (3)	17.6% (6)	6.3% (2)	10.6% (11)
Dyskinesia	5.9% (2)	8.3% (3)	14.7% (5)	3.1% (1)	9.6% (10)
Asthenia	5.9% (2)	8.3% (3)	2.9% (1)	12.5% (4)	5.8% (6)
Pollakiuria	5.9% (2)	8.3% (3)	2.9% (1)	0.0% (0)	5.8% (6)
Mental impairment	2.9% (1)	11.1% (4)	8.8% (3)	9.4% (3)	7.7% (8)
Listless	0.0% (0)	11.1% (4)	8.8% (3)	0.0% (0)	6.7% (7)
Blood urea increased	0.0% (0)	11.1% (4)	5.9% (2)	6.3% (2)	5.8% (6)
Weight decreased	0.0% (0)	8.3% (3)	8.8% (3)	3.1% (1)	5.8% (6)
Anxiety	0.0% (0)	8.3% (3)	8.8% (3)	3.1% (1)	5.8% (6)
Depressed mood	0.0% (0)	5.6% (2)	11.8% (4)	0.0% (0)	5.8% (6)

The number in the parentheses indicates the number of patients; CK, creatine kinase.

#### **4.(ii).A.(2) Late phase II/phase III study (Data 5.3.5.1-2, Study AD810N-204-5 [January to December 2004])**

A randomized, double-blind study was conducted to investigate the efficacy, safety, and dose response of zonisamide in patients with Parkinson's disease who have not responded sufficiently to the treatment with L-DOPA preparation (target sample size, 320 subjects [80 per group]) in 58 study sites in Japan. The administration period, which followed a 2-week run-in period, consisted of a 12-week treatment period and a 2-week dose reduction period. During the treatment period, zonisamide (25, 50, or 100 mg) or placebo was administered orally once daily and, during the dose-reduction period, zonisamide was administered orally once daily at half the dose used in the treatment period (in the 25 mg group, 25 mg was administered without dose reduction).

The inclusion criteria were the same as those in the phase II study except for the rule about the patient's self-entry in the symptom diary being possible. The rules related to concomitant treatments were also the same.

Of 347 randomized patients (84 in the zonisamide 25 mg group, 87 in the 50 mg group, 87 in the 100 mg group, 89 in the placebo group), 330 patients (79 patients, 85 patients, 83 patients, 83 patients) excluding 17 patients who did not take the study drug during the treatment period were included in the safety analysis. Of them, 326 patients (77 patients, 85 patients, 82 patients, 82 patients) except 4 patients who were excluded because of missing evaluation data after study drug administration in the treatment period were included in FAS and handled as the primary efficacy analysis population. In addition, a total of 312 patients (74 patients, 81 patients, 76 patients, 81 patients) excluding 7 patients with insufficient treatment period, 5 patients with poor compliance, 5 patients with violation of exclusion criteria, and 4



patients with violation of concomitant drugs/therapies (including duplicate counting) were included in PPS.

As for efficacy, the change in the UPDRS Part III total score at the final assessment from baseline (at the end of the run-in period), the primary endpoint, was  $-6.3 \pm 0.8$  (least squares mean  $\pm$  SE; ANCOVA with treatment group as factor and baseline value as covariate) in the 25 mg group,  $-5.8 \pm 0.8$  in the 50 mg group,  $-4.6 \pm 0.8$  in the 100 mg group, and  $-2.0 \pm 0.8$  in the placebo group, showing a significant difference between the 25 mg group and the placebo group and between the 50 mg group and the placebo group ( $P = 0.001$  and  $0.003$ , respectively; Dunnett-type test). Similar results were obtained with PPS. Using an ANCOVA model with treatment group as the factor and baseline value as the covariate, a contrast test for 4 dose-response patterns was carried out. As a result,  $P$  value was the smallest at the contrast coefficient that results in the saturation of the effect at a low dose (placebo:25 mg:50 mg:100 mg =  $-3:1:1:1$ ) ( $P < 0.001$ ). The change in ON time at the final assessment from baseline (at the end of the run-in period) in patients who showed wearing-off phenomenon, one of the secondary endpoints, was  $0.190 \pm 2.650$  (mean  $\pm$  SD) in the 25 mg group,  $1.290 \pm 2.591$  in the 50 mg group,  $1.563 \pm 2.863$  in the 100 mg group, and  $0.349 \pm 1.941$  in the placebo group.

As for safety, the incidence and the number of adverse events were 70.9% (56 of 79) of patients (164 events) in the 25 mg group, 72.9% (62 of 85) of patients (195 events) in the 50 mg group, 79.5% (66 of 83) of patients (204 events) in the 100 mg group, and 65.1% (54 of 83) of patients (153 events) in the placebo group. The following table shows adverse events reported by  $\geq 5\%$  of patients in any group. No death occurred, whereas serious adverse events were observed in 2.5% (2 of 79) of patients in the 25 mg group (depressed level of consciousness and pyrexia in 1 patient each), 2.4% (2 of 85) of patients in the 50 mg group (compression fracture and granulocyte count decreased in 1 patient each), 3.6% (3 of 83) of patients in the 100 mg group (dermatitis medicamentosa/toxic skin eruption, weight decreased, and femoral neck fracture in 1 patient each), and 2.4% (2 of 83) of patients in the placebo group (pyrexia/hyponatraemia/depressed level of consciousness, and blood creatinine increased/blood urea increased/renal dysfunction in 1 patient each).

**Table. Adverse event reported by  $\geq 5\%$  of patients in any group**

	25 mg (N = 79)	50 mg (N = 85)	100 mg (N = 83)	Placebo (N = 83)
Contusion	10.1% (8)	3.5% (3)	4.8% (4)	3.6% (3)
Blood CK increased	8.9% (7)	8.2% (7)	4.8% (4)	8.4% (7)
Listless	7.6% (6)	7.1% (6)	10.8% (9)	6.0% (5)
Weight decreased	7.6% (6)	3.5% (3)	9.6% (8)	4.8% (4)
Constipation	6.3% (5)	8.2% (7)	4.8% (4)	3.6% (3)
Blood urea increased	6.3% (5)	1.2% (1)	4.8% (4)	2.4% (2)
Decreased appetite	5.1% (4)	8.2% (7)	16.9% (14)	14.5% (12)
ALT increased	5.1% (4)	4.7% (4)	4.8% (4)	0.0% (0)
Depressive symptom	5.1% (4)	3.5% (3)	6.0% (5)	4.8% (4)
Insomnia	5.1% (4)	3.5% (3)	4.8% (4)	4.8% (4)
Diarrhoea	5.1% (4)	3.5% (3)	0.0% (0)	0.0% (0)
Malaise	5.1% (4)	2.4% (2)	3.6% (3)	1.2% (1)
Dizziness postural	3.8% (3)	5.9% (5)	7.2% (6)	7.2% (6)
Nasopharyngitis	2.5% (2)	9.4% (8)	4.8% (4)	6.0% (5)
Nausea	2.5% (2)	3.5% (3)	6.0% (5)	3.6% (3)
Somnolence	1.3% (1)	15.3% (13)	15.7% (13)	4.8% (4)
Pyrexia	1.3% (1)	5.9% (5)	2.4% (2)	4.8% (4)
Thirst	1.3% (1)	2.4% (2)	7.2% (6)	2.4% (2)

The number in the parentheses indicates the number of patients; ALT, alanine aminotransferase.

#### **4.(ii).A.(3) Phase III study (Data 5.3.5.1-3, Study AD810N-303-8 [■ to ■ 20■])**

A randomized, double-blind study was conducted to compare the efficacy of zonisamide with placebo in patients with Parkinson's disease in progression stage who were being treated with L-DOPA preparation and have not responded sufficiently to the current treatment (target sample size, 150 subjects [50 per group]) in 31 study sites in Japan. The administration period, which followed a 2-week run-in period, consisted of a 12-week treatment period. During the run-in period, placebo was administered orally once daily and, during the treatment period, zonisamide (25 or 50 mg) or placebo was administered orally once daily.

The main inclusion criteria were patients aged  $\geq 20$  and  $< 75$  years who (1) showed UPDRS Part III total score of  $\geq 10$ , (2) had been treated with L-DOPA preparation for  $\geq 6$  months (26 weeks) and responded to the treatment during the early phase of the treatment, (3) but became less responsive to L-DOPA preparation, and was currently receiving the treatment with other antiparkinsonian drugs in addition to L-DOPA preparation.

Patients had to receive other antiparkinsonian drugs in combination with L-DOPA preparation. Concomitant use of zonisamide preparation, other unapproved drugs, or study drug was prohibited. Changing the dosage regimen was prohibited from 4 weeks before the start of the run-in period for the following drugs, if used: antiparkinsonian drugs including L-DOPA preparation, antihypertensive drugs, neuropsychiatric drugs, etc. that may affect the symptoms of Parkinson's disease.

Of 196 randomized patients (64 in the zonisamide 25 mg group, 66 in the 50 mg group, 66 in the placebo group), 189 patients (63 patients, 63 patients, 63 patients) excluding 7 patients who did not receive the study drug during the treatment period were included in the safety analysis. A total of 185 patients (61 patients, 61 patients, 63 patients), excluding 11 patients (11 without efficacy data during the treatment period and 3 with violation of inclusion criteria, duplicate counting included) were included in FAS and handled as the primary efficacy analysis population. Of them, a total of 179 patients (59 patients, 57

patients, 63 patients), excluding 6 patients (4 with insufficient treatment period, 1 with violation of exclusion criteria, 1 with protocol violation that could affect efficacy assessment), were included in PPS.

The primary efficacy endpoint was the change in the UPDRS Part III total score at the final assessment from baseline (at the end of the run-in period). The least squares mean  $\pm$  SE of the UPDRS Part III total score at the final assessment (ANCOVA with treatment group as the fixed effect and baseline UPDRS Part III total score as the covariate) was  $-5.9 \pm 0.9$  in the 25 mg group,  $-5.5 \pm 0.9$  in the 50 mg group, and  $-2.9 \pm 0.9$  in the placebo group, showing a significant difference between the 25 mg group and the placebo group ( $P = 0.029$ , Dunnett-type test). In the investigation of the dose response of the change in the UPDRS Part III total score at the final assessment from baseline, a contrast test for 3 dose-response patterns was carried out using an ANCOVA model with treatment group as the fixed effect and baseline UPDRS Part III total score as the covariate. As a result,  $P$  value was the smallest at the contrast coefficient that results in the saturation of the effect at a low dose (placebo:25 mg:50 mg =  $-2:1:1$ ) ( $P = 0.010$ ).

As for safety, the incidence and the number of adverse events were 55.6% (35 of 63) of patients (79 events) in the 25 mg group, 60.3% (38 of 63) of patients (86 events) in the 50 mg group, and 65.1% (41 of 63) of patients (97 events) in the placebo group. The following table shows adverse events reported by  $\geq 5\%$  of patients in any group. Death occurred in 1 patient (sudden death) in the 25 mg group. Serious adverse events including death were observed in 6 patients in the 25 mg group (6 events; sudden death, hallucination, cellulitis, bronchopneumonia, hypoglycaemic unconsciousness, and urinary tract infection in 1 patient each), 3 patients in the 50 mg group (4 events; weight decreased, femoral neck fracture, and blood alkaline phosphatase [ALP] increased/prostate cancer in 1 patient each), and 2 patients in the placebo group (3 events; pyrexia/rash, and cervical vertebral fracture in 1 patient each). Adverse events leading to discontinuation of study drug administration were observed in 4 patients (4 events) in the 25 mg group, 5 patients (6 events) in the 50 mg group, and 2 patients (2 events) in the placebo group.

**Table. Adverse events reported by  $\geq 5\%$  of patients in any group**

	25 mg (N = 63)	50 mg (N = 63)	Placebo (N = 63)
Insomnia	4.8% (3)	4.8% (3)	7.9% (5)
Nasopharyngitis	4.8% (3)	3.2% (2)	11.1% (7)
Blood CK increased	4.8% (3)	1.6% (1)	6.3% (4)
Decreased appetite	4.8% (3)	1.6% (1)	6.3% (4)
Contusion	3.2% (2)	0% (0)	6.3% (4)
Constipation	1.6% (1)	1.6% (1)	6.3% (4)
Weight decreased	0% (0)	4.8% (3)	6.3% (4)

The number in the parentheses indicates the number of patients.

#### **4.(ii).A.(4) Long-term treatment study (1) (Data 5.3.5.2-1, Study AD810N-203-2 [20 to 20])**

An open-label study was conducted to investigate the efficacy and safety in the long-term administration in combination of zonisamide with L-DOPA preparation in 44 patients with Parkinson's disease who, after having completed the phase II study, wished to continue administration, in 23 study sites in Japan.

After a trial-run period of 2 to 4 weeks administering zonisamide (50 mg), zonisamide (50-200 mg) was administered orally once daily for 48 to 52 weeks.

Concomitant use of zonisamide preparation, other unapproved drugs, and study drugs was prohibited. As for the drugs restricted in the phase II study, they were allowed at the same dosage regimen as that used at the end of the phase II study, but newly starting concomitant use was prohibited.

All of 44 patients enrolled in the study were included in the safety analysis and FAS. Of them, 42 patients excluding 2 patients with insufficient treatment period were included in PPS, and handled as the primary efficacy analysis population. A total of 32 patients received the study drug for  $\geq 26$  weeks, and of them, 26 patients for 52 weeks. The maximum daily dose was 50 mg in 11.9% (5 of 42) of patients, 100 mg in 31.0% (13 of 42) of patients, 150 mg in 28.6% (12 of 42) of patients, and 200 mg in 28.6% (12 of 42) of patients, with the number of patients evenly distributed over the maximum daily dose range of 100 to 200 mg.

The mean treatment period in PPS was  $305.5 \pm 113.2$  days (mean  $\pm$  SD). The last daily dose was 50 mg/day in 38.1% (16 of 42) of patients, 100 mg/day in 33.3% (14 of 42) of patients, 150 mg/day in 9.5% (4 of 42) of patients, and 200 mg/day in 19.0% (8 of 42) of patients. The maximum daily dose was 50 mg/day in 11.9% (5 of 42) of patients, 100 mg/day in 31.0% (13 of 42) of patients, 150 mg/day in 28.6% (12 of 42) of patients, and 200 mg/day in 28.6% (12 of 42) of patients.

As for efficacy, the UPDRS Part III total score decreased from baseline up to 4 to 28 weeks after the start of administration. In patients showing wearing-off phenomenon, ON time increased from the run-in period in the phase II study up to 4 to 36 weeks after the start of administration.

As for safety, adverse events were observed in 88.6% (39 of 44) of patients (269 events). The following table shows adverse events reported by  $\geq 5\%$  of patients. No death occurred, whereas serious adverse events were observed in 6 patients (1 event each of thoracic vertebral fracture, ileitis, appendicitis, excitability, hallucination, confusional state, depressed mood, listless, delusion, irritability, abnormal behaviour, calculus urinary, ileus, constipation, pneumonia, gastroenteritis, abdominal pain, inappetence, diarrhoea, headache, nausea, and vomiting).

**Table. Adverse events reported by  $\geq 5\%$  of patients**

	(N = 44)
Nasopharyngitis	31.8% (14)
Somnolence	22.7% (10)
Constipation	18.2% (8)
Thirst	18.2% (8)
Dizziness postural	15.9% (7)
Nausea	13.6% (6)
Abnormal gait	13.6% (6)
Headache	13.6% (6)
Mental impairment	13.6% (6)
Depressed mood	13.6% (6)
Hallucination	13.6% (6)
Stomach discomfort	11.4% (5)
Pyrexia	11.4% (5)
Anxiety	11.4% (5)
Listless	11.4% (5)
Inappetence	9.1% (4)
Dyskinesia	9.1% (4)
Malaise	6.8% (3)
Oedema peripheral	6.8% (3)
Weight decreased	6.8% (3)
Blood ALP increased	6.8% (3)
Insomnia	6.8% (3)
Rash	6.8% (3)

The number in the parentheses indicates the number of patients.

#### **4.(ii).A.(5) Long-term treatment study (2) (Data 5.3.5.4-1, Study AD810N-302-6 [20 to 20])**

A multi-center, open-label study was conducted to investigate the safety and efficacy of zonisamide in long-term administration in combination with L-DOPA preparation in patients with Parkinson's disease (target sample size, 70 subjects) in 6 study sites in Japan. Zonisamide was administered orally once daily at an appropriate dose within the range from 25 to 100 mg.

The main inclusion criteria were patients aged  $\geq 20$  and  $< 80$  years who had been receiving L-DOPA preparation at a fixed dosage regimen for  $\geq 4$  weeks before the start of the study.

Concomitant use of zonisamide preparation, other unapproved drugs, and study drug was prohibited, while other drugs were permitted. All of 92 patients receiving the study drug were included in the safety analysis. Of them, 90 patients except 2 patients without data were included in FAS and handled as the primary efficacy analysis population. A total of 83 patients, excluding 7 patients with insufficient treatment period, violation of inclusion criteria, etc., were included in PPS.

The mean duration of administration in FAS was  $291.9 \pm 126.2$  days (mean  $\pm$  SD). The last daily dose was 25 mg/day in 72.2% (65 of 90) of patients, 50 mg/day in 23.3% (21 of 90) of patients, 75 mg/day in 3.3% (3 of 90) of patients, and 100 mg/day in 1.1% (1 of 90) of patients. The maximum daily dose was 25 mg/day in 31.1% (28 of 90) of patients, 50 mg/day in 47.8% (43 of 90) of patients, 75 mg/day in 16.7% (15 of 90) of patients, and 100 mg/day in 4.4% (4 of 90) of patients, with approximately 80% of patients treated at the daily dose of  $\leq 50$  mg/day.

The efficacy was investigated based on the parameter values relative to those at baseline (immediately before the start of administration). The UPDRS Part III total score decreased at all evaluation time points from 4 weeks after the start of administration up to the time of final evaluation.

As for safety, a total of 554 adverse events were observed in 94.6% (87 of 92) of patients. The following table shows adverse events reported by  $\geq 5\%$  of patients. Death occurred in 1 patient (cardio-respiratory arrest). It was suspected that dysphagia associated with Parkinson's disease caused aspiration pneumonia, which in turn caused respiratory acidosis, hyperkalaemia, and finally cardio-respiratory arrest, and the causal relationship of the study drug to death was ruled out. Serious adverse events other than deaths were observed in 8 patients (lipoma, cardiomyopathy, depressed level of consciousness, pneumonia, cerebral haemorrhage, and gastric cancer in 1 patient each, femoral neck fracture/fall in 1 patient, and anaemia/haemoglobin decreased/haematocrit decreased/red blood cell count decreased in 1 patient). The causal relationship to the study drug was ruled out for all of them except fall, and all events disappeared or resolved.

**Table. Adverse events reported by  $\geq 5\%$  of subjects**

	(N = 92)
Back pain	23.9% (22)
Nasopharyngitis	22.8% (21)
Constipation	17.4% (16)
Somnolence	17.4% (16)
Decreased appetite	14.1% (13)
Dyskinesia	12.0% (11)
Listless	12.0% (11)
Nausea	9.8% (9)
Contusion	9.8% (9)
Depression	9.8% (9)
Hallucination	9.8% (9)
Insomnia	9.8% (9)
Oedema	8.7% (8)
Weight decreased	8.7% (8)
Dizziness	8.7% (8)
Dizziness postural	8.7% (8)
Eczema	8.7% (8)
Headache	7.6% (7)
Arthralgia	7.6% (7)
Pyrexia	6.5% (6)
Haematocrit decreased	6.5% (6)
Haemoglobin decreased	6.5% (6)
Red blood cell count decreased	6.5% (6)
Diarrhoea	5.4% (5)
Stomatitis	5.4% (5)
Thirst	5.4% (5)
Laryngopharyngitis	5.4% (5)
ALT increased	5.4% (5)
AST increased	5.4% (5)
Blood lactate dehydrogenase increased	5.4% (5)
Inappetence	5.4% (5)
Neck, shoulder and arm syndrome	5.4% (5)

The number in the parentheses indicates the number of patients; AST, aspartate aminotransferase.

**4.(ii).A.(6) Extended treatment study (Reference data) (Data 5.3.5.4-2, Study AD810N-301-4 [ongoing since ■■■ 20■■■])**

A multi-center, open-label study was conducted to investigate the safety and efficacy of long-term treatment with zonisamide in combination with L-DOPA preparation in patients with Parkinson's disease who had completed the long-term treatment study (1), the long-term treatment study (2), the late phase II/phase III study, or the phase III study and wished for extended treatment, in 4 study sites in Japan. Zonisamide was administered orally once daily at 25 to 100 mg which was to be adjusted as appropriately. If the patient had received zonisamide at a dose exceeding 100 mg/day before transitioning to this study, patients were allowed to take zonisamide up to that dose (maximum dose 200 mg).

Concomitant use of zonisamide preparation, other unapproved drugs, and study drug was prohibited.

A total of 28 patients were enrolled by ■■■, 20■■■. Of these, 13 patients discontinued the study and 15 patients are continuing the treatment. The duration from the start of the study drug administration to ■■■, 20■■■ or study discontinuation was 1666 days (ongoing) at the maximum and 27 days at the minimum. The maximum daily dose of the study drug was 200 mg in 2 patients, 150 mg in 2 patients, 100 mg in 5 patients, 75 mg in 5 patients, 50 mg in 9 patients, and 25 mg in 5 patients.

A total of 153 adverse events occurred in 25 of 28 patients by ■■■, 20■■■. Main adverse events included common cold, CK increased, insomnia, weight decreased, low back pain, and dyskinesia. Serious adverse events (dysphoria/vomiting/blood pressure decreased in 1 patient, neutropenia/white blood cell count decreased/segmented cell decreased in 1 patient, depressed state [suicide attempt suspected]/consciousness disturbed [acute drug intoxication] in 1 patient, inguinal hernia/ilium fracture in 1 patient, sleep attacks/lumbar spine compression fracture in 1 patient, and head fracture after left hip replacement, prostate cancer, aggravation of visual hallucination, pneumonia aspiration, and haemoglobin decreased in 1 patient each) were observed in 10 patients.

**4.(ii).B Outline of the review by PMDA**

**4.(ii).B.(1) Background of conducting the phase III study**

The data of clinical studies submitted for application had problems described below and, as a result, study patients were not selected appropriately and the proposed dose was determined based on insufficient evidence. PMDA concluded it necessary to conduct a confirmatory study including the investigation of dose response, upon clarifying the patient population appropriate for treatment with zonisamide, based on the expected clinical positioning of zonisamide. PMDA therefore asked the applicant to conduct an additional clinical study, to which the applicant agreed and conducted the phase III study.

Problems with study patients

Patients enrolled in the late phase II/phase III study were “patients showing wearing-off phenomenon,” “patients who became less responsive to L-DOPA preparation,” and “patients who were hesitating to increase the dose of L-DOPA because of adverse drug reactions.” (a) In patients without decrease in response to L-DOPA preparation, the change in the UPDRS Part III total score at the final assessment

from baseline, the primary endpoint, was  $-5.6 \pm 1.2$  (least squares mean  $\pm$  SE) in the 25 mg group,  $-4.5 \pm 1.0$  in the 50 mg group, and  $-3.6 \pm 1.1$  in the 100 mg group, failing to show significant improvement at any dose compared with the placebo group ( $-4.0 \pm 1.0$ ), with the distribution of the change similar to that observed in the placebo group. (b) There were only a small number of patients who were hesitating to increase the dose of L-DOPA preparation because of adverse drug reactions. As a result, it was difficult to evaluate the appropriateness of treatment with zonisamide in this patient group. (c) Despite the fact that the mechanism of action of zonisamide has not necessarily been clarified, the study was conducted without restriction of concomitant drugs. As a result, the possibility could not be excluded that the difference in the concomitant drugs affected the efficacy assessment. Thus, the study failed to clarify the patient population appropriate for treatment with zonisamide.

#### Problems with efficacy

In the late phase II/phase III study, the absolute value of the change in the UPDRS Part III total score, the primary endpoint, decreased with the increase in dose, whereas one of the secondary endpoints, wearing-off time (change in ON time, change in the percentage of ON time, change in OFF time, and change in the percentage of OFF time) improved in a dose-dependent manner. These results indicate that the study on the dose response of zonisamide is insufficient and that the parameter for assessing the efficacy of zonisamide is unclear.

#### **4.(ii).B.(2) Clinical positioning**

PMDA asked the applicant to describe the patient population appropriate for treatment with zonisamide, and, based on the description, explain the appropriateness of the patients investigated in the additional phase III study.

The applicant's explanation:

In the phase II study and the late phase II/phase III study targeting "patients with Parkinson's disease in progression stage who have not responded sufficiently to the treatment with L-DOPA preparation," patients who met either of the following criteria were enrolled: (1) "Patients showing wearing-off phenomenon," (2) "patients who became less responsive to L-DOPA preparation," and (3) "patients who were hesitating to increase the dose of L-DOPA because of adverse drug reactions." In the phase III study, in order to allow more clear evaluation of the efficacy of zonisamide, "patients who became less responsive to L-DOPA preparation" were selected as target patients, for the following reason: Thus, among the 3 patient groups [(1), (2), and (3) above] enrolled in the phase II study and in the phase II/phase III study, the patient group (2) showed a greater change in the absolute value of the change in the UPDRS Part III total score in the zonisamide group compared with the placebo group. Also, the following inclusion criteria were adopted regarding the concomitant drugs: (1) "Patients who had been treated with L-DOPA preparation for  $\geq 6$  months and responded to the treatment during the early phase of the treatment," and (2) "patients who were currently receiving the treatment with other antiparkinsonian drugs in addition to L-DOPA preparation." In addition, as the criterion for "patients who have not responded sufficiently to treatment," "patients with the UPDRS Part III total score of  $\geq 10$  immediately before the start of the run-in period" was adopted. The applicant considered that these restrictions would ensure the enrollment of "patients with Parkinson's disease in progression stage who



have not responded sufficiently to the combined treatment with L-DOPA preparation and other antiparkinsonian drugs, showing persistent motor dysfunction (symptoms).”

PMDA asked the applicant to explain the clinical positioning of zonisamide, based on the target patients used in the phase III study.

The applicant’s response:

The basic treatment of patients with Parkinson’s disease in progression stage is, in addition to administration of L-DOPA preparation, to add other antiparkinsonian drugs according to the characteristics of the drugs and the patient’s conditions. Consequently, multiple antiparkinsonian drugs are concomitantly administered to patients with Parkinson’s disease in progression stage in clinical settings. In the placebo-controlled studies conducted without restriction on concomitant use with antiparkinsonian drugs (phase II study, late phase II/phase III study, and phase III study) as well, most of patients have not responded sufficiently to the treatment with L-DOPA preparation received other antiparkinsonian drugs (3.2 different types of drugs on average) in addition to L-DOPA preparation. In light of the observations that zonisamide was demonstrated to be effective in the late phase II/phase III study and in the phase III study, zonisamide is effective in patients with Parkinson’s disease in progression stage who have not responded sufficiently even to the standard therapy of the current medical level, and therefore that additional concomitant use with zonisamide is one of the useful treatment options in clinical settings.

PMDA’s view:

The proposed target patients for zonisamide are “patients with Parkinson’s disease in progression stage who have not responded sufficiently to the combined treatment with L-DOPA preparation and other antiparkinsonian drugs, showing persistent motor dysfunction (symptoms).” Given that Parkinson’s disease is a progressive disease and that, in clinical settings, there are patients who have not responded sufficiently even to combinations of multiple antiparkinsonian drugs, there is a medical need for a drug that is expected to improve motor dysfunction. The inclusion criteria adopted in the additional phase III study were appropriate for selecting the target patients for the treatment with zonisamide, and this study demonstrated the superiority of the 25 mg group to the placebo group in the efficacy. It is therefore expected that zonisamide has a certain level of efficacy as a drug for patients with Parkinson’s disease in progressive stage who have not responded sufficiently to L-DOPA preparation administered in combination with other antiparkinsonian drugs.

#### **4.(ii).B.(3) Efficacy and dose response relationship**

In the late phase II/phase III study, the absolute value of the change in the total UPDRS Part III total score, the primary endpoint, decreased with the increase in dose, whereas one of the secondary endpoints, wearing-off time (change in ON time, change in the percentage of ON time, change in OFF time, and change in the percentage of OFF time) increased in a dose-dependent manner. Based on these findings, the applicant used the UPDRS Part III total score as the primary efficacy endpoint in the phase III study. PMDA asked the applicant to explain the appropriateness of adopting this endpoint.

The applicant's response:

UPDRS Part III scores, which include items that evaluate 4 major symptoms of Parkinson's disease, i.e., tremor, rigidity, akinesia, and gait disturbance, are endpoints appropriate for evaluating the efficacy of drugs that are expected to improve the motor activity of patients with Parkinson's disease by increasing dopamine level. Zonisamide improved the UPDRS Part III total score in all placebo-controlled studies in a similar manner, and the dose-response relationship observed in the 3 studies was consistent to one another. As for change in ON time, change in the percentage of ON time, change in OFF time, and change in the percentage of OFF time, all of which are associated with wearing-off phenomenon, were also considered to be useful as the efficacy endpoints for zonisamide, but no consistent results were obtained among these studies. The above results suggested that the UPDRS Part III total score which objectively evaluates the motor activity of each patient is best-suited as the efficacy endpoint for zonisamide, and is thus appropriate as the primary endpoint.

PMDA's view:

It is acceptable that the applicant considered that zonisamide is expected to be effective in improving motor activity from the results of the phase II and late phase II/phase III studies and used the UPDRS Part III total score as the primary endpoint in the phase III study.

The efficacy of zonisamide against wearing-off phenomenon was not investigated in the phase III study. Wearing-off phenomenon was used as one of the inclusion criteria in the phase II and the late phase II/phase III studies and investigated as a secondary endpoint in an exploratory manner, but not sufficiently evaluated. As a result, the efficacy of zonisamide against wearing-off phenomenon is unclear from the data submitted in the present application.

Zonisamide is approved as an antiepileptic drug, albeit at different doses. PMDA asked the applicant to explain the possibility that the UPDRS Part III total score improved as a result of improvement in specific sub-items of the UPDRS Part III.

The applicant's response:

Examination of changes in each sub-score of the UPDRS Part III scores in the zonisamide group of the placebo-controlled studies showed that zonisamide was effective on a wide range of sub-items without showing bias on specific sub-items, depending on the severity of the symptoms at the administration. These results suggest that the improvement of the UPDRS Part III total score by zonisamide is not dependent on the improvement of some specific sub-items.

PMDA considers it appropriate to conclude that there are patients with Parkinson's disease in whom zonisamide is effective although the mechanism of action of the drug remains unclear, for the following reasons: (1) The improvement of the UPDRS Part III total score by zonisamide is not dependent solely on the improvement of some specific sub-items, and (2) the superiority of the 25 mg group to the placebo group was demonstrated in the phase III study in patients presenting with various symptoms included in sub-items.

In the phase II and late phase II/phase III studies submitted at the application, the efficacy of zonisamide, assessed by the UPDRS Part III total score, tended to decrease with the increase in dose. Similarly, in the additional phase III study, although the 25 mg group was shown to be superior to the placebo group in the improvement of the UPDRS Part III total score, the primary endpoint, superiority of the 50 mg group to the placebo group was not confirmed, failing to demonstrate the increase in the efficacy with the increase in dose. Regarding the failure of the UPDRS Part III total score to show dose response, the applicant argued that zonisamide-induced dyskinesia, etc., may have possibly affected the motor activity and, at high doses, aggravated UPDRS Part III score, the index for motor activity. PMDA asked the applicant to explain the appropriateness of this argument.

The applicant's response:

In the late phase II/phase III study and the phase III study, adverse drug reactions associated with increased dopamine level, one of the pharmacological actions of zonisamide, occurred, suggesting that they may possibly affect the motor activity or evaluation thereof. In order to investigate the possibility that UPDRS Part I (mental function, behavior, and mood) and UPDRS Part IV (A. Dyskinesia), the items evaluating adverse drug reactions related to increased dopamine level, and adverse events during the treatment period (psychiatric disorder and dyskinesia) had a combined effect, the total changes in the UPDRS Part III score at the final assessment in the late phase II/phase III study and in the phase III study were investigated in subpopulations stratified by the presence of occurrences or aggravations of 1 or more of any of the above 4 items. The results showed that, in the subpopulation with occurrences/aggravations, the absolute change was smaller in the 100 mg group than in the 25 and 50 mg groups in the late phase II/phase III study and smaller in the 50 mg group than in the 25 mg in the phase III study. In the subpopulation without occurrences/aggravations, the change was similar between all the zonisamide groups in both studies. These results suggest that, with the increase in dopamine level which is supposedly one of the pharmacological actions of zonisamide, dyskinesia or psychiatric symptoms occurred, affecting the change in the UPDRS Part III total score, an index of locomotor activity, and it may be a cause of which a dose-dependent efficacy had not be shown.

PMDA's view:

The explanation of the applicant falls short of explaining both of the following at the same time: (1) The efficacy of zonisamide tended to decrease at higher doses than 25 mg and (2) there were patients who responded to zonisamide not at 25 mg but at 50 mg. Thus, the cause of the lack of dose response has not been clarified. However, since zonisamide was shown to be effective at least at a dose of 25 mg both in the late phase II/phase III study and in the phase III study, it is appropriate to conclude that the dose of 25 mg is an effective dose. Whether it is appropriate to accept 50 mg as another effective dose is further discussed in the next section.

#### **4.(ii).B.(4) Dosage and administration**

In the phase III study, only the 25 mg group was shown to be superior to the placebo group. Therefore, PMDA asked the applicant to explain the appropriateness of including zonisamide 50 mg in the dosage and administration.

The applicant's response:

In the long-term treatment study (2) which started with zonisamide 25 mg, the dose was increased to 50 mg in 51 patients. Of them, the UPDRS Part III total score improved in 21 of 30 patients in whom assessment data were available both before dose increase (assessment during 25 mg administration) and after dose increase. The UPDRS Part III total score improved by  $\geq 5$  in 13 patients and by  $\geq 10$  in 5 patients. In the late phase II/phase III study, the UPDRS Part III total score improved by  $\geq 25$  in 1 patient in the 50 mg group and in 4 patients in the 25 mg group and, in the phase III study, the score improved by  $\geq 15$  in 5 patients in the 50 mg group and in 8 patients in the 25 mg group, showing that marked efficacy was observed in a slightly larger number of patients in the 25 mg group than in the 50 mg group, but the variation in the efficacy was significantly large (late phase II/phase III study,  $-6.7 \pm 8.5$  in the 25 mg group,  $-5.7 \pm 7.3$  in the 50 mg group; phase III study,  $-5.8 \pm 7.8$  in the 25 mg group,  $-5.7 \pm 6.8$  in the 50 mg group; mean  $\pm$  SD). Furthermore, the analysis of response rate (percentage of patients who showed  $\geq 30\%$  improvement in the UPDRS Part III total score from baseline) showed that the percentage was slightly higher in the 50 mg group than in the 25 mg group (late phase II/phase III study, 38.2% [29 of 76] of patients in the 25 mg group, 45.1% [37 of 82] of patients in the 50 mg group; phase III study, 41.0% [25 of 61] of patients in the 25 mg group, 45.8% [27 of 59] of patients in the 50 mg group).

These results suggest that there are patients who have not responded sufficiently to zonisamide 25 mg but have UPDRS Part III total score improved after dose increase to 50 mg, thus benefiting from the treatment. Given that Parkinson's disease is progressive with no established curative therapy at the current medical level, providing the treatment option of "the dose of zonisamide increase to 50 mg" is considered to be clinically useful. Taking account of the above discussions, the proposed dosage and administration, i.e., "The usual adult dosage is 25 to 50 mg of zonisamide administered orally once daily" is changed to "The usual adult dosage is 25 mg of zonisamide administered orally once daily. The dose may be increased up to 50 mg once daily if 25 mg is not sufficiently effective."

PMDA's view:

In the phase III study in which the target patients appropriate for evaluating the efficacy of zonisamide more accurately were reselected by new criteria, only the 25 mg group was shown to be superior to the placebo group in the primary endpoint (change in the UPDRS Part III total score at the final assessment from baseline). Therefore, the dose of zonisamide is recommended to be 25 mg. As for 50 mg, on the other hand, it is difficult to say that there is any evidence to support the claim that a higher efficacy is achieved by increasing the dose from 25 mg to 50 mg, given the following: (1) 50 mg has not been shown to be superior to the placebo group, (2) it is unclear which patient population is expected to respond favorably to the dose increase, and (3) the total UPDRS Part III total score did not improve with dose increase in the late phase II/phase III study either.

PMDA asked the applicant to explain a possibility that zonisamide is effective at doses below 25 mg taking into account that the absolute change in the UPDRS Part III total score decreased with the increase in the dose of zonisamide.

The applicant's response:

The change in the UPDRS Part III total score is similar between 25 mg and 50 mg, and the absolute value was larger compared with the placebo group. This result suggests that the dose-response curve reached the plateau at the dose of 25 to 50 mg of zonisamide, which in turn suggests that the clinical effect is expected within this dose range, and it is considered unnecessary to investigate recommended doses which are lower than the above dose range from the aspect of both safety and efficacy, for the following reasons: (a) In placebo-controlled studies, the incidence of adverse events occurred in the 25 mg group and the 50 mg group is similar to that in the placebo group, showing a high safety profile of zonisamide within this dose range; (b) results of placebo-controlled studies showed that zonisamide 25 mg and zonisamide 50 mg were both effective to a similar extent for the treatment of Parkinson's disease; (c) when patients who responded to the UPDRS Part III total score in the late phase II/phase III study and the phase III study were subjected to analysis, a higher efficacy was observed in the 50 mg group than in the 25 mg group; (d) in patients who have not responded sufficiently to zonisamide 25 mg in the long-term treatment study (2), dose increase to 50 mg improved the UPDRS Part III total score, providing clinical benefit for the treatment of Parkinson's disease.

PMDA's view:

Efficacy of zonisamide at doses below 25 mg was not investigated at all, and the reason for claiming that the antiparkinsonian effect of zonisamide levels off at 25 to 50 mg is unclear. Therefore, the possibility cannot be excluded that zonisamide is effective at lower doses as well. Under ordinary circumstances, the dose-response should have been investigated with lower doses included. Nevertheless, it is of clinical significance that the efficacy of 25 mg was confirmed in the additional phase III study in the appropriate patient population selected according to the rigorous criteria.

Judging from the submitted clinical data, PMDA considers that the dosage and administration should be "The usual adult dosage is 25 mg of zonisamide administered orally once daily." The decision will be finalized, taking account of comments raised in the Expert Discussion.

#### **4.(ii).B.(5) Indication**

In the phase III study which investigated the efficacy of zonisamide, L-DOPA preparation was administered to all patients, and there are no data that show the efficacy of zonisamide in patients with Parkinson's disease not receiving L-DOPA preparation. Also, the superiority of zonisamide to placebo was demonstrated in patients have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs. Therefore, PMDA considers that the proposed indication "Parkinson's disease (for patients who have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)" is appropriate. The decision will be finalized, taking account of comments raised in the Expert Discussion.

#### **4.(ii).B.(6) Safety**

##### **4.(ii).B.(6).1 Neuroleptic malignant syndrome**

In the placebo-controlled study, there were patients who showed increased CK following administration of zonisamide. PMDA asked the applicant to explain whether the patients had neuroleptic malignant

syndrome, to discuss the risk of zonisamide-induced neuroleptic malignant syndrome, and to provide the applicant's view on the necessity of advising caution.

The applicant's explanation:

In the placebo-controlled studies, there were 29 subjects with abnormal CK level. However, almost all of them were free from pyrexia and other symptoms suggestive of neuroleptic malignant syndrome. It is therefore unlikely that there were patients with neuroleptic malignant syndrome except patients who were actually reported to have neuroleptic malignant syndrome. However, since there were 3 patients (1 patient each in the 50, 100, and 200 mg groups) with neuroleptic malignant syndrome (or suspected neuroleptic malignant syndrome) in the phase II study, the risk of zonisamide inducing the disease cannot be ruled out. Taking account of the facts that neuroleptic malignant syndrome occurred in the phase II study, and that neuroleptic malignant syndrome is one of the serious adverse drug reactions of antiparkinsonian drugs, neuroleptic malignant syndrome is included in the "2. Important Precautions" section and the "4. Adverse Reactions (1) Clinically significant adverse reactions" section of the package insert (proposed).

PMDA's view:

Neuroleptic malignant syndrome is well known as a significant adverse event requiring caution in treatment with antiparkinsonian drugs. In the clinical studies on zonisamide as well, neuroleptic malignant syndrome was observed and its causal relationship to the study drug could not be ruled out. It is therefore necessary to advise caution and thus the applicant's action is appropriate.

#### **4.(ii).B.(6).2) Hallucination, delusion**

Hallucination and delusion were reported as adverse events that were serious or led to treatment discontinuation in many patients. Therefore, PMDA asked the applicant to explain the relationship between these adverse events and the mechanism of action and the dose of zonisamide.

The applicant's explanation:

It is highly likely that hallucination and delusion were induced by the dopamine level-increasing effect of zonisamide. In the placebo-controlled study, the incidence of these adverse events by treatment group was as follows: The incidence of hallucination was 2.8% (5 of 178) of patients in the placebo group, 2.8% (4 of 142) of patients in the 25 mg group, and 2.7% (5 of 182) of patients in the 50 mg group, showing similar frequency of occurrences, but 5.0% (6 of 119) of patients in the 100 mg group and 17.6% (6 of 34) of patients in the 200 mg group, showing a dose-dependent increase. In the phase III study, the incidence of hallucination was 1.6% (1 of 63) of patients in the placebo group, 3.2% (2 of 63) of patients in the 25 mg group, and 3.2% (2 of 63) of patients in the 50 mg group, but none of them discontinued the treatment. No delusion occurred.

PMDA's view:

In the clinical studies in patients with Parkinson's disease, the incidence of events related to psychiatric disorders including hallucination and delusion tends to increase in a dose-dependent manner although the incidence is not clearly higher in the 25 mg group compared with the placebo group. Also, the causal relationship to zonisamide could not be ruled out for many of the affected patients. It is therefore

necessary to advise caution that attention should be paid to psychiatric symptoms in treatment with zonisamide and that the administration should be discontinued if they have occurred. Taking account of the facts that the incidence of hallucination was higher than that observed in the treatment for the approved indication of epilepsy and that the event is reported for other antiparkinsonian drugs as well, the applicant has included psychiatric symptoms such as hallucination, delusion, confusion, and delirium in the “4. Adverse Reactions (1) Clinically significant adverse reactions” section of Precaution in the package insert (proposed). PMDA considers that there are no particular problems with the measures taken by the applicant.

#### **4.(ii).B.(6).3) Relationship with concomitant drugs**

Since zonisamide is intended to be used in combination with a levodopa-containing drug and other antiparkinsonian drugs, PMDA asked the applicant to explain whether there were adverse events requiring caution in combination with any specific antiparkinsonian drug and, in particular, whether any specific concomitant drug was involved in death or serious adverse events.

The applicant’s explanation:

As for relationship with concomitant drugs, the incidences of adverse events were investigated separately for patients receiving different doses of L-DOPA preparation and for use and non-use of other concomitant antiparkinsonian drugs (dopamine agonists, MAO-B inhibitors, amantadine, anticholinergic drugs, or droxidopa) in the combined data of 5 studies [phase II study, late phase II/phase III study, phase III study, long-term treatment study (1), and long-term treatment study (2)]. When the daily dose of L-DOPA preparation was classified into  $\leq 1000$  mg/day, 1001 to 2000 mg/day, and  $\geq 2001$  mg/day, the incidence of adverse events and the treatment discontinuation due to adverse events increased with the increase in the dose of L-DOPA preparation. The increase in the incidence of adverse events associated with the increase in the dose of L-DOPA preparation was observed in the placebo group as well, suggesting that the increase in the incidence was highly likely due to the increase in the dose of L-DOPA preparation per se. As for the incidences of adverse events in patients treated with or without concomitant antiparkinsonian drug, the incidence of adverse events was higher in patients treated with a concomitant dopamine agonist or droxidopa than in patients treated without these drugs, and the same results were observed in the placebo group as well. There were no individually observed adverse events requiring any special attention. For other antiparkinsonian drugs, their use or non-use did not cause any consistent tendency in the incidence of adverse events. As for 39 patients who died or had serious adverse events, serious adverse events reported by  $\geq 3$  patients among those receiving zonisamide were hallucination in 4 of 613 patients, delusion in 3 of 613 patients, femoral neck fracture in 3 of 613 patients, and pneumonia in 3 of 613 patients. As for hallucination, 3 of the 4 affected patients had received zonisamide with amantadine. Therefore, the incidence of hallucination, regardless of serious or not, was investigated separately for patients treated with or without concomitant amantadine. As a result, the incidence was similar between patients treated with and without amantadine, failing to show the effect of amantadine. Thus, there were no adverse events requiring caution in combination with any specific antiparkinsonian drugs. Based on the above, there is no safety problem in administering zonisamide in combination with other antiparkinsonian drugs.

PMDA's view:

Among serious adverse events, hallucination was observed frequently in amantadine co-administration group. Therefore, it is not appropriate to conclude that concomitant use with amantadine has no safety problem. Also, since there are various combinations of antiparkinsonian drugs that may possibly be concomitantly administered with zonisamide, information on the safety of zonisamide should be collected continuously after the market launch. However, there is little need to provide caution for concomitant use with any specific antiparkinsonian drugs currently, and accepted the explanation of the applicant.

#### **4.(ii).B.(7) Post-marketing surveillance, etc.**

PMDA's view:

Given that the target patients for zonisamide are patients who have not responded sufficiently to a levodopa-containing drug even in combination with other antiparkinsonian drugs, it is expected that zonisamide is concomitantly administered with multiple antiparkinsonian drugs over a long-term period. Therefore, it is necessary to collect information on the safety and efficacy of zonisamide (including the information on the type of the concomitant drugs, change in the dose, addition, or discontinuation of the concomitant drugs, etc.) during a long-term administration in clinical use. The applicant has submitted a plan for the post-marketing specified use-results survey aimed at collecting the information on the safety and efficacy in long-term use (sample size 500, standard follow-up period 1 year). Appropriateness of the sample size, the standard follow-up period, and detailed evaluation items will be finalized, taking account of comments raised in the Expert Discussion.

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

#### **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 Pharmaceutical Affairs Act. As a result, there were no particular problems. On the basis of the inspection and assessment, PMDA concluded that there should be no obstacles to conducting its review based on the application documents submitted.

#### **2. PMDA's conclusion concerning the results of the on-site GCP inspection**

The new drug application data (5.3.1.2-3, 5.3.1.2-4, 5.3.5.1-1, 5.3.5.1-2, 5.3.5.2-1, 5.3.5.4.1-1, 5.3.5.1-3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Pharmaceutical Affairs Act. As a result, it was found out that, in some study sites, physicians did not attend a meeting of the institutional review board on the continuation of the study in patients with serious and unexpected adverse drug reactions reported by the sponsor. It was also found out that it took  $\geq 1$  month to transmit part of the information on adverse drug reactions from the sponsor to the investigator and the head of the medical institution, as required by Article 273 of the Enforcement Ordinance of the Pharmaceutical Affairs Act. However, PMDA concluded that there should be no obstacles to conducting its review based on the application documents submitted.



#### **IV. Overall Evaluation**

As a result of the review described above, PMDA concluded that the data submitted demonstrate the efficacy and safety of zonisamide in the treatment of patients with Parkinson's disease (for patients who have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs).

As for the efficacy, the UPDRS Part III total score, the primary endpoint in the phase III study, demonstrated the superiority of the 25 mg group to the placebo group, confirming the efficacy of zonisamide 25 mg.

As for the safety, patients in the zonisamide 25 mg group in the phase III study showed no adverse events of particular problems compared to those observed in the placebo group, and the incidence of adverse events was not significantly different between the groups, indicating that there are no major safety problems with zonisamide 25 mg.

The dose of zonisamide, provision of information for the proper use of zonisamide, and the appropriate details of investigations after marketing will be finalized, account of comments raised in the Expert Discussion.

## Review Report (2)

November 12, 2008

### I. Product Submitted for Approval

<b>Brand Name</b>	Trerief Tablets 25 mg (changed from Tremode Tablets 25 mg [proposed name])
<b>Non-proprietary Name</b>	Zonisamide
<b>Applicant</b>	Dainippon Pharmaceutical Co., Ltd. (currently Dainippon Sumitomo Pharma Co., Ltd.)
<b>Date of Application</b>	September 28, 2005 (marketing application for a drug)

### II. Content of the Review

PMDA sought the expert advisors' comments based on the Review Report (1). Discussions with the expert advisors and results are outlined below

The expert advisors attending the Expert Discussion declared that the product submitted for approval does not come under the Section 1 or 2 (1) of "Tentative Rules for Addressing Conflict of Interest for the External Experts of the Pharmaceuticals and Medical Devices Agency" dated May 8, 2007.

#### 1. Clinical positioning

The phase III study demonstrated the superiority of zonisamide 25 mg to placebo. Zonisamide is expected to improve motor dysfunction in patients with Parkinson's disease in an advanced stage who have inadequate response to L-DOPA preparations administered in combination with other antiparkinsonian drugs. In the clinical setting, there are patients who have not responded adequately even to multiple antiparkinsonian drugs. Given these, zonisamide can meet clinical needs, and this conclusion was supported by the expert advisors. The expert advisors also made the following comment on the add-on effect of zonisamide to L-DOPA preparations and other antiparkinsonian drugs: For patients with Parkinson's disease with inadequate improvement in motor dysfunction, an improvement in any one of the UPDRS Part III scores is a significant change. Zonisamide 25 mg improved the change in the UPDRS Part III total score that was 3 points greater than with placebo ( $-5.8 \pm 7.8$  in the 25 mg group,  $-2.8 \pm 6.8$  in the placebo group; mean  $\pm$  SD), which is clinically significant.

#### 2. Dosage and administration

PMDA has concluded that the dosage and administration for zonisamide be "The usual adult dosage is 25 mg of zonisamide administered orally once daily." In response, the expert advisors raised the following comments: (1) The results of the phase III study or other clinical studies did not demonstrate dose-responsive efficacy of zonisamide, failing to provide evidence to support the dose increase to 50 mg, and (2) in the comparison with the placebo group in the phase III study, a significant effect was

observed in the 25 mg group but not in the 50 mg group. Therefore, it is reasonable, in a strict sense, to recommend only 25 mg.

At the same time, the expert advisors also raised the following comments:

- In the late phase II/phase III study, a significant difference was observed between the 50 mg group and the placebo group in efficacy. Therefore, the 50-mg dose may also be recommended on the premise that a post-marketing clinical study is conducted to demonstrate the effect of dose increase to 50 mg.
- Among patients in whom the dose was increased from 25 mg to 50 mg in the long-term treatment study (2),  $\geq 40\%$  of patients who had evaluable UPDRS Part III total score, both pre-and post-dose increase, showed improvement of  $\geq 5$  points, which is considered to be highly clinically significant. In addition, no significant difference was observed in the incidences of adverse events between the 25 mg group and the 50 mg group. Patients who are benefited by an optional dose increase up to 50 mg will outnumber those who are adversely affected, if dose increase to 50 mg is allowed, on the premise that which patient population benefits from the dose increase is to be identified after approval.
- The action of zonisamide cannot be explained solely from the blood concentration, and each patient has different optimal dose. Thus the dose increase to 50 mg may further improve the symptoms of some patients. Furthermore, in the late phase II/phase III study, the wearing-off phenomenon improved in the 50 mg group. The wearing-off phenomenon is the most critical concern in some patients. Considering no marked increase in adverse drug reactions when the dose was increased to 50 mg, the dose up to 50 mg should preferably be approved and verified further via a post-approval clinical study. The efficacy of zonisamide at doses below 25 mg should be closely investigated as well.

PMDA's view:

In the phase III study in patients who were considered appropriate to evaluate the efficacy of zonisamide more precisely, the zonisamide 50 mg group failed to show superiority to the placebo group in the primary endpoint (change from baseline in the UPDRS Part III total score at the final evaluation). In addition, the absolute value of the UPDRS Part III total score decreased with the dose increase both in the late phase II/phase III study and in the phase III study. Furthermore, the action mechanism of zonisamide remains unclear. Given these, the clinical significance of increasing the dose of zonisamide is unclear, precluding the approval of the dose of 50 mg. The long-term treatment study (2) was an open-label study without the control group. It is therefore difficult to evaluate the additional effect of dose increase to 50 mg based on the data from the study. The phase II study and the late phase II/phase III study failed to yield consistent results on zonisamide's positive effect on the wearing-off phenomenon, which was, thus not evaluated in the phase III study. As a result, the data attached to the present application do not demonstrate the efficacy of zonisamide on the wearing-off phenomenon clearly. Therefore, the dose of 50 mg should not be added to the dosage regimen for the present application unless the efficacy of dose increase to 50 mg is demonstrated in a separate clinical study.

The expert advisors comments:

- Enhanced efficacy by dose increase from 25 mg, even if any, will be expected in only a limited number of patients. The approval of 50 mg, may lead to careless dose increase for any non-responders

to 25 mg. In the situation with unknown patient population benefiting from dose increase, it is reasonable to approve only 25 mg for the present application.

- There are various points remaining unclear, namely, (1) the yet unclear action mechanism of zonisamide, (2) patient population expected to respond to 50 mg, (3) efficacy at doses below 25 mg yet to be evaluated, and (4) the relationship between blood zonisamide concentration and efficacy that has not been clarified despite zonisamide's long elimination half-life, which takes many days before reaching a steady state. These unclear factors precludes the evaluation of the efficacy of zonisamide 50 mg.

The expert advisors finally supported the PMDA's conclusion that, for the present application, the dosage regimen of "the usual adult dosage is 25 mg of zonisamide administered orally once daily."

Also, the expert advisors noted that it is of clinical significance to conduct a clinical study to investigate the additional effect of increasing to 50 mg and the efficacy of doses below 25 mg even after the approval of zonisamide 25 mg.

Taking account of the discussion at the Expert Discussion, PMDA instructed the applicant to change the dosage regimen, and asked their view on conducting a clinical study to investigate the effect of dose increase to 50 mg and the efficacy of doses below 25 mg and considering the addition of these doses based on study results.

The applicant's response:

All of the clinical studies investigating the efficacy and safety of zonisamide (phase II study, late phase II/phase III study, phase III study, long-term treatment study [1], and long-term treatment study [2]) were conducted in patients receiving L-DOPA preparations, and the patients were required to take L-DOPA preparations together with zonisamide. Therefore, the dosage regimen is modified as described below, also taking account of the results of the above discussions. Clinical studies to investigate the effect of dose increase to 50 mg and the efficacy of doses below 25 mg will be conducted as needed with consideration given to the following: (1) the patient population which is expected to respond to zonisamide increased to 50 mg, (2) a study design that will demonstrate the effect of dose increase, (3) the appropriateness of investigating the efficacy of doses below 25 mg, (4) development of lower dose formulation(s), and (5) the feasibility of conducting the study, including the study size.

[Dosage and administration (original)]

The usual adult dosage is 25 mg of zonisamide administered orally once daily. The dose may be increased up to 50 mg once daily if 25 mg is not sufficiently effective.

[Dosage and administration (modified)] (Underline denotes change.)

Zonisamide should be administered concomitantly with levodopa-containing drugs.

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

PMDA accepted the above response of the applicant.

### 3. Indication

While some expert advisors supported the PMDA's conclusion that the indication for zonisamide should be "Parkinson's disease (for patients who have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs), the others noted the following:

- The PMDA's conclusion is basically rational. However, in the clinical setting, some patients are compelled to discontinue antiparkinsonian drugs because of gastrointestinal adverse drug reactions such as nausea, neuropsychiatric adverse drug reactions such as hallucination and delusion, or involuntary movement such as dyskinesia. Given the concomitant use of L-DOPA preparations is essential, the use of zonisamide should also be allowed for "patients who cannot use other concomitant antiparkinsonian drugs due to adverse reactions" instead of limiting to "those who have not responded adequately to levodopa-containing drugs even in combination with other antiparkinsonian drugs."
- The concomitant use of L-DOPA preparations with a dopamine agonist is common. However, ergot dopamine agonists may cause cardiac valvulopathy, and non-ergot dopamine agonists may cause sleepiness, etc., thus they are not suitable for many patients. Therefore, preferably, the target patients of zonisamide should not be limited to "those who are taking L-DOPA preparations with other antiparkinsonian drugs," but should include "those taking only L-DOPA preparations," in whom the efficacy of zonisamide was suggested in the late phase II/phase III study.

PMDA's view:

In the phase II study and in the late phase II/phase III study, L-DOPA preparation alone was concomitantly administered to only a small number of patients (0 of 132 patients and 5 of 326 patients [1.5%], respectively, in FAS), with almost all patients in both studies receiving 2 or more concomitant drugs (3.3 and 3.2 drugs, respectively, on average). Therefore, basically, "patients who have not responded adequately to levodopa-containing drugs even in combination with other antiparkinsonian drugs" are appropriate target patients for the treatment with zonisamide. However, the indication should be determined by taking account of the above comment of the expert advisors as well as their another advice that refers to the difficulty in the clinical setting to enroll patients receiving only L-DOPA preparations in a clinical study on drugs other than dopamine agonist targeting patients with Parkinson's disease.

Accordingly, PMDA asked the applicant to consider defining the indication that will not exclude patients in the clinical setting who once used to receive an antiparkinsonian drug concomitantly with L-DOPA preparation but later discontinued the antiparkinsonian drug, consequently receiving the L-DOPA preparation alone.

In response, the applicant modified the indication as shown below.

[Indication (original)]

Parkinson's disease (for patients who have not responded adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)

[Indication (revised)] (Underline denotes change.)

Parkinson's disease (for patients who did not respond adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)

PMDA accepted the response of the applicant.

#### 4. Safety

The following conclusions of PMDA were supported by the expert advisors: (1) Adverse events that occurred at a high incidence in the zonisamide group in each clinical study are known adverse drug reactions of zonisamide in patients with epilepsy, (2) appropriate precautions are advised in the package insert (proposed) against neuroleptic malignant syndrome, which is an adverse event requiring particular caution in using zonisamide as an antiparkinsonian drug, and against hallucination, which occurred more frequently in patients with Parkinson's disease than in the approved use for epilepsy. At present, no further advice is required on the safety of zonisamide in patients with Parkinson's disease. The following conclusion of PMDA was also supported by the expert advisors: Since there are varieties of possible combinations of antiparkinsonian drugs to be administered with zonisamide, safety data of zonisamide should be collected continuously after the market launch. However, there is little need to provide new cautionary advice on the concomitant use of zonisamide with any specific antiparkinsonian drugs currently.

The expert advisors commented that it is clear that zonisamide is used in combination with multiple antiparkinsonian drugs, the pharmacokinetic interactions of zonisamide with multiple antiparkinsonian drugs should not be left unknown and be investigated after the marketing approval. Accordingly, PMDA asked the applicant to closely review the blood zonisamide concentration data of the phase II study and the long-term treatment study (1) and to explain whether multiple concomitant antiparkinsonian drugs may affect the blood zonisamide concentration.

The applicant's response:

Among the patients subjected to the population pharmacokinetics analysis (90 patients) in the phase II study (dose of zonisamide, 50-200 mg), patients who received other antiparkinsonian drugs in addition to L-DOPA preparations and zonisamide were subjected to analysis of the effect of multidrug therapy on the clearance (CL/F) of zonisamide. Data on each of other antiparkinsonian drugs used in addition to an L-DOPA preparation and zonisamide were examined, and combination patterns of 2 other antiparkinsonian drugs that had been used for  $\geq 3$  patients were identified. For each drug of the combination patterns identified, CL/F of zonisamide of patients who used the antiparkinsonian drug was compared with that of patients who did not. The ratio of the estimated mean CL/F of individual patients who used both of the 2 drugs paired to that of those who did not use either one of the 2 drugs ranged 0.918 to 1.36. Similarly, combination patterns of  $\geq 3$  antiparkinsonian drugs used in addition to L-DOPA preparations and zonisamide were examined. The ratio of the estimated mean CL/F of individual patients who used all of the 3 drugs combined to that of those who used none of the 3 drugs ranged 0.954 to 1.31. Furthermore, another similar analysis was performed on 29 patients whose CL/F was estimated in the long-term treatment study (1) (dose of zonisamide, 50-200 mg). The ratio of the estimated mean CL/F of individual patients who used both of the 2 drugs paired to that of those who did not use either one of

the 2 drugs ranged 0.992 to 1.43, showing no specific tendency in the values as compared with the ratios observed in the combination patterns in the phase II study.

Thus, the close examination of the data of the phase II study and the long-term treatment study (1) showed no significant variations in CL/F of zonisamide depending on concomitant antiparkinsonian drugs administered in different combinations in addition to L-DOPA preparations. This suggests that the blood zonisamide concentration is unlikely to be affected by the combination patterns of concomitant drugs.

PMDA's view:

Although it is necessary to continuously collect information on the safety of the multidrug therapy in the post-marketing surveillance, the pharmacokinetic interactions between zonisamide and multiple antiparkinsonian drugs are unlikely to pose a clinical problem, judging from the submitted data. If, after the approval, a clinical study of any type is conducted, it should also aim to investigate the effect of concomitant use of various antiparkinsonian drugs on the blood zonisamide. These conclusions of PMDA were supported by the expert advisors.

## 5. Food effect

A single dose of the final formulation of zonisamide (25 mg) was administered orally under fasting conditions or after a meal to 12 Japanese healthy adult men (6/group) by a 2-period cross-over design (washout period, 21 days).  $C_{\max}$  was  $0.1177 \pm 0.0185$  (mean  $\pm$  SD) and  $0.0959 \pm 0.0137$   $\mu\text{g/mL}$ , respectively,  $\text{AUC}_{0-t}$  was  $6.683 \pm 1.574$  and  $5.392 \pm 1.764$   $\mu\text{g}\cdot\text{h/mL}$ , respectively, and  $T_{1/2}$  was  $94.049 \pm 26.276$  and  $138.670 \pm 139.200$  hours, respectively. Median  $T_{\max}$  was 4.0 hours in both groups. No adverse events were observed. No clinically significant problems were observed in laboratory test values, vital signs, body weight, electrocardiogram, or medical examination (subjective symptoms and objective findings), either after administration under fasted conditions or after administration under fed conditions.

The applicant's explanation:

The least squares geometric mean ratio (90% CI) of  $C_{\max}$  and  $\text{AUC}_{0-t}$  after administration under fed conditions to that after administration under fasted conditions was 81.60% (76.24%-87.34%) and 78.85% (71.25%-87.25%), respectively. Thus, despite a tendency toward decreased  $C_{\max}$  and  $\text{AUC}_{0-t}$  by food consumption, food has little effect on the bioavailability of zonisamide.

Based on the dose-proportional pharmacokinetics of zonisamide observed within the dose range investigated for the previous approval (100-400 mg) and that in patients with Parkinson's disease (50-200 mg/day at steady state), the applicant explained at the time of application that it would be possible to estimate the pharmacokinetics within the dose range of 25 to 50 mg/day in patients with Parkinson's disease. However, according to the data submitted with the application,  $C_{\max}$  and  $\text{AUC}_{0-t}$  after a single dose of zonisamide at the clinical dose of 25 mg were less than dose-proportional when (1) compared to  $C_{\max}$  ( $0.86 \pm 0.12$   $\mu\text{g/mL}$ ) and  $\text{AUC}_{0-t}$  ( $52.3 \pm 7.4$   $\mu\text{g}\cdot\text{h/mL}$ ) after a single dose of 100 mg (Data 5.3.1.2-4) and (2) compared to  $C_{\max}$  (3.31  $\mu\text{g/mL}$ , relative standard deviation 11.7%) and  $\text{AUC}_{\infty}$  (220.8  $\mu\text{g}\cdot\text{h/mL}$ , relative standard deviation 14.1%) after a single dose of 300 mg (Data 5.3.3.4-2). PMDA asked the applicant to explain the reason for these conflicting results.

The applicant's response:

The relationship between dose and  $AUC_{\infty}$  after single-dose administration was analyzed at the dose range from 25 to 300 mg using a power model.  $AUC_{\infty}$  was 14.7  $\mu\text{g}\cdot\text{h}/\text{mL}$  after a single dose of 25 mg and 94.3  $\mu\text{g}\cdot\text{h}/\text{mL}$  after a single dose of 100 mg, showing a roughly dose-proportional increase, based on which the bioavailability and  $CL/F$  were assumed not to differ significantly among the doses. Also,  $T_{\text{max}}$  was comparable in each of the above studies, suggesting that the difference in the absorption rate among different doses would be minor. On the other hand, the distribution of zonisamide in red blood cells is suggested to become partially saturated at approximately  $\geq 3 \mu\text{g}/\text{mL}$  (Data F-4 submitted for the previous approval). Because  $C_{\text{max}}$  of the dose range of 25 to 200 mg is  $< 3 \mu\text{g}/\text{mL}$ , the lower is the dose, the lower is the distribution rate in red blood cells expected, resulting in an increased distribution volume when zonisamide is administered in a single dose within this dose range (25-200 mg).

PMDA's view:

The applicant's explanation may suggest one possible theory but does not adequately explain the reason why  $C_{\text{max}}$  after a single dose of 25 mg was less than dose-proportional as compared with  $C_{\text{max}}$  after a single dose of 100 mg. Nevertheless, it is of clinical significance that the pharmacokinetics of zonisamide at the clinical dose of 25 mg and the food effect on the pharmacokinetics was investigated in a clinical study in Japanese patients. The study results should therefore be communicated via the package insert.

## **6. Post-marketing surveillance, etc.**

PMDA's view:

Zonisamide is intended for patients who "did not respond adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs," and thus is expected to be used together with multiple antiparkinsonian drugs for a long-term period, safety and efficacy (including the types of concomitant drugs and their dose changes) data of zonisamide in long-term treatment should be collected from the post-marketing clinical setting. These conclusions of PMDA were supported by the expert advisors. In addition, the expert advisors noted that the administration of some of antiparkinsonian drugs may need be discontinued before treatment with zonisamide, and thus information on prior medications should also be collected.

Accordingly, PMDA instructed the applicant to submit an outline of the surveillance plan that allows to collect information relevant to the above appropriately.

The applicant's response:

A specified use-results survey will be conducted on patients with a diagnosis of Parkinson's disease who are new to zonisamide (excluding patients with a history of treatment with zonisamide [even as an antiepileptic drug]). The survey period is 2 years 6 months, the standard follow-up period is 1 year, and the target sample size is 500. Information to be collected about the previous antiparkinsonian drugs includes drug names, whether discontinued or continued at the start of zonisamide, and the reason of discontinuation, if any. Information to be collected about the concomitant antiparkinsonian drugs includes drug names, dosage regimen, duration of use, and the reason for dose change or discontinuation,



if any. Information to be collected about zonisamide includes the dosage regimen, duration of use, and the reason for dose change or discontinuation, if any.

PMDA considers that the outline of the submitted study protocol and the survey plan need to be further reviewed in detail, but concluded that the response of the applicant is generally acceptable.

### **7. Dissolution specifications and shelf life of the drug product**

As reported earlier, the applicant proposed to revise the dissolution test specifications of the drug product from “dissolution rate [REDACTED] in [REDACTED] minutes, [REDACTED] in [REDACTED] minutes,” which were initially submitted, to “dissolution rate [REDACTED] in [REDACTED] minutes, [REDACTED] in [REDACTED] minutes,” which were based on the study drug. PMDA, because the difference in the dissolution performance between the initially submitted specifications and the study drug-based specifications does not significantly affect the efficacy or safety of zonisamide, concluded that the change to the study drug-based dissolution specifications was acceptable. This conclusion of PMDA was supported by the expert advisors.

Also, taking account of the observations that the observed dissolution rate up to 12 months in the long-term testing and the estimated dissolution rate up to 24 months meet the study drug specifications, PMDA concluded that it is appropriate to determine the shelf life of zonisamide as 24 months.

## **III. Overall Evaluation**

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and the dosage and administration, and that the result is subject to further deliberation by the First Committee on New Drugs.

Since the product submitted for approval is a drug with a new indication, the re-examination period is 4 years.

The product is classified as a powerful drug, and is not classified as a biological product or a specified biological product.

### **Indication**

Parkinson’s disease (for patients who did not respond adequately to a combination of levodopa-containing drugs with other antiparkinsonian drugs)

### **Dosage and administration**

Zonisamide should be concomitantly administered with a levodopa-containing drug.  
The usual adult dosage is 25 mg of zonisamide administered orally once daily.